ANNALS OF THE RHEUMATIC DISEASES

RHEUMATOID ARTHRITIS AND POLYARTERITIS NODOSA

BY

JOHN BALL

From the Rheumatism Research Centre, University of Manchester

(RECEIVED FOR PUBLICATION JULY 28, 1954)

Structural arterial lesions are not usually considered to play an important part in the pathogenesis of rheumatoid arthritis; and in many histological descriptions of necropsy or biopsy material significant arterial lesions are not mentioned even when the vascular system has been carefully scrutinized (Bennett and others, 1940; Baggenstoss and Rosenberg, 1943; Fingerman and Andrus, 1943; Bennett, 1943; Collins, 1949).

In muscle biopsies, Sokoloff and others (1951) found a mild arteritis (in which fibrinoid alteration or fibrosis was not a conspicuous feature) in five of 57 cases of rheumatoid arthritis; and Cruickshank (1952), also examining skeletal muscle, encountered a "subacute arteritis without any necrosis of the vessel walls" only occasionally in a large series of cases. In a recent necropsy study of 72 cases of rheumatoid arthritis, Cruickshank (1954) found arteritis in eighteen. In seven of these there was rheumatic carditis and the arteritis was mainly confined to the heart; in the remainder there was no rheumatic heart disease and the arterial lesions (which in nine were not confined to the heart) were described as "rheumatoid arteritis" and claimed to be distinguishable from polyarteritis nodosa.

On the other hand, Dawson (1940) mentioned in an editorial comment that he had seen three patients with rheumatoid arthritis who were shown to have polyarteritis nodosa at necropsy, and some recent clinical studies draw attention to this type of case. Nyström (1953) described three patients in whom polyarteritis nodosa was detected some years after the onset of progressive rheumatoid disease; and Bauer and others (1952), in a patient diagnosed as suffering from typical rheumatoid arthritis of 2 years' duration, observed the development of eosinophilia, and skin nodules in which biopsy revealed arterial lesions indistinguishable from polyarteritis nodosa. According to Friedman and others (1953), a deforming multiple arthritis, commonly misdiagnosed as rheumatoid arthritis, may herald the onset of polyarteritis nodosa. These authors used the term "pararheumatic arthropathy" to describe such cases, implying, presumably, that the joint changes are based on articular polyarteritis nodosa, though no histological evidence of this is presented in their paper.

Unfortunately, histological studies of the articular tissues in polyarteritis nodosa are extremely rare. Numerous clinical investigations have shown that symptoms referable to the joints are common in this syndrome, but, according to Jones (1942) and Lowman (1952), the disability is of a minor order and "objective evidence of arthritis" is rare. Nevertheless a history of polyarthritis is not infrequently encountered in the published case reports. Rose (1953), using strict clinical criteria, found a polyarthritis indistinguishable from rheumatoid arthritis in eight of 104 histologically proven cases of polyarteritis nodosa; in seven the arthritis preceded and in the remaining case it developed during the course of polyarteritis nodosa. Three further cases of typical rheumatoid arthritis, in which a firm clinical diagnosis of polyarteritis nodosa was made but in which the available pathological material did not provide complete proof, were excluded from his analysis.

It would appear, then, that a small minority of patients classified as suffering from rheumatoid arthritis, and a minority of patients classified as suffering from polyarteritis nodosa, show features of both syndromes. It is the purpose of this communication to describe the clinical and pathological aspects of five cases illustrating this association.

Material and Methods

In addition to the five cases reported here, subcutaneous and tendon nodules from 46 cases of rheumatoid arthritis, and biopsies of the articular tissues in a

further 25 cases, were examined to determine the type and incidence of arterial lesions.

It may be said at once that polyarteritis nodosa was never seen in articular biopsies, and was found (mainly in arterioles) in only four of the 46 nodules, usually in close association with generalized inflammation of the connective tissues.

Tissues were fixed in 4 per cent. formaldehyde in 0·9 per cent. saline and stained in one or more of the following ways: haemalum and eosin; phosphotungstic acid haematoxylin; Lillie's method for reticulin; Van Gieson's stain; various elastic stains; the Masson-Goldner and the periodic acid-Schiff-orange G (Pearse, 1950) trichrome methods.

In all cases various joints were removed *in toto*, and, after fixation and freezing, they were hemisectioned or cut into slabs with the band saw. Radiographs were taken of selected slabs, which were then double-embedded in low viscosity nitrocellulose and paraffin wax. The heart was routinely examined by taking several blocks after the manner of Gross and others (1930).

In the period during which the present five cases were encountered, fifteen other cases of rheumatoid arthritis were examined without finding arteritis.

Diagnostic Criteria

The clinical features and course of rheumatoid arthritis vary considerably and in some instances the differential diagnosis from other types of polyarthritis is difficult. Nevertheless the character and distribution of the polyarthritis and the occurrence of subcutaneous nodules and vasospasm, together with characteristic radiological appearances and a positive sheep cell agglutination test (Ball, 1952), enable one to recognize a typical case. Patients presenting clinical or pathological features suggestive of disseminated lupus erythematosus, scleroderma, or dermatomyositis, in which arteritis is sometimes found, have been excluded from the present study.

Rheumatoid arthritis was diagnosed histologically in the presence of an inflammatory erosion of articular cartilage and subchondral bone by pannus, the appearance of which varied from a non-specific granulation tissue to a fibrous nodule depending on the activity and duration of the disease process.

Polyarteritis nodosa was defined as a segmental

TABLE I

CLINICAL FINDINGS AND FINAL DIAGNOSIS

Case No.	1	2	3	4	5
Sex	Male	Female	Male	Male	Female
Age	64	64	62	50	53
Duration of Illness (yrs)	1	1 5/12	2½	13	1 1/12
Type of Arthropathy	Rapidly progressive; destructive multiple arthritis	Moderately severe; progressive multiple arthritis	Severe; progressive multiple arthritis	Severe deforming multiple arthritis	Mild transient multiple arthritis
X-ray Findings	Severe articular erosions	Minor articular erosions	Severe articular erosions	Gross joint destruction with deformity	Juxta-articular osteoporosis only
Rheumatoid Nodules	Both elbows	Nil	Elbows, sacrum, occiput, scapulae, fingers	Both elbows	Nil
Skin Rashes	None	None	None	None	None
Differential Sheep Cell Agglutination Test	Positive	Not done	Positive	Positive	Negative
White Blood Cells (per c.mm.)	15,000	9,200 10,000	28,100	3,500 5,000 5,600	9,200 21,600 19,800
Treatment	Gold; intravenous iron; aureomycin	Gold; penicillin; radical mastectomy	Gold; antibiotics; anticoagulants; *cortisone*	Gold	Penicillin; digitalis; *cortisone*
Drug Sensitivity	Some distress after iron	Nil	Nil	Nil	Nil
Clinical Diagnosis	Rheumatoid arthritis	Rheumatoid arthritis; polyarteritis nodosa suspected shortly before death	Rheumatoid arthritis	Rheumatoid arthritis	Polyarteritis nodosa
Pathological Diagnosis	Rheumatoid arthritis and polyarteritis nodosa	Rheumatoid arthritis and polyarteritis nodosa	Rheumatoid arthritis and polyarteritis nodosa	Rheumatoid arthritis and polyarteritis nodosa	Polyarteritis nodosa and rheumatoid arthritis

destructive inflammatory lesion, characterized, in the acute phase, by a fibrinoid alteration of the vessel wall with or without aneurysm formation or thrombosis and, in the healing phase, by degrees of replacement fibrosis. The cellular infiltration is variable and often pleomorphic though giant cells are exceptional. The lesions most commonly occur in small or medium-sized arteries, but vessels of any calibre may be affected.

General Description of Cases

The principal clinical and pathological findings are presented in Tables I and II. Cases 1 to 4 may be considered together because in general they were closely similar clinically and pathologically. The patients were all elderly subjects who were considered on clinical and radiological grounds to have had typical rheumatoid arthritis for periods varying from 1 to 13 years; only in Case 2, in which peripheral neuritis was first noticed 7 weeks before death, was there a definite suspicion of polyarteritis nodosa in life. Three had rheumatoid subcutaneous nodules and the sheep cell agglutination test (D.A.T.) was positive in the three cases tested. None presented clinical evidence of rheumatic heart disease or definite signs of disseminated lupus erythematosus. At necropsy polyarteritis nodosa was found in addition to changes in the joints characteristic of rheumatoid arthritis. Examination of the affected joints showed that the articular vessels were commonly but not always involved, and for this reason (and others which will be discussed later) it was concluded that the arthritis *per se* was not a direct result of articular polyarteritis nodosa. These four cases are presented as illustrating the occurrence of polyarteritis nodosa as a complication of rheumatoid arthritis.

Case 5 presented an example of polyarteritis nodosa, diagnosed as such in life and confirmed at necropsy. Some time after the onset of the illness, there developed a mild multiple arthritis of rheumatoid type which virtually disappeared 3 months later after the commencement of cortisone therapy for the arteritis. In spite of the transient nature of the arthropathy there was typical histological evidence of rheumatoid arthritis in an inactive phase, the articular vessels being normal.

TABLE II
HISTOLOGICAL FINDINGS

Case No.	Joints Examined	Rheumatoid Changes	Polyarteritis Nodosa in			Other Lesions
			Joint Capsule	Peri-articular Tissue	Viscera	
1	1st M.P.	Early severe	–	+	Kidneys Pancreas Stomach Small intestine Hilus of lung	Intestinal ulceration Peritonitis Fibrinous pleurisy Basal meningitis
	Wrist	Early severe	–	+		
	Carpus	Early severe	–	+		
	Elbow	Early moderate	+	+		
2	1st M.P.	Moderate	–	+	Myocardium Liver Kidneys Adrenals Small intestine Peripheral nerves	Focal peritonitis Fibrinous pericarditis
	Prox. I.P.	Moderate	–	–		
	Dist. I.P.	Moderate	–	–		
	Knee	Moderate	–	+		
3	1st M.P.	Moderate	–	–	Liver Kidneys Spleen Pancreas Duodenum	Skin ulceration Atheromatous coronary thrombosis Renal infarcts Pneumonia
	Sternoclavicular	Moderate	–	–		
	Atlanto-axial	Severe advanced	–	–		
	Cervical interfacetal	Early mild	–	+		
4	Radiocarpal	Advanced	+	+	Pancreas Liver Spleen Kidneys Intestine Myocardium	Haemorrhagic pericarditis Myocardial fibrosis
	Sternoclavicular	Advanced	–	–		
	Cervical interfacetal	Mild	–	+		
5	1st M.P.	Early mild	–	–	Liver Kidneys Intestine Pancreas Adrenals Omentum	Mitral stenosis Pericarditis "Rheumatic pneumonia"
	Prox. I.P.	Early mild	–	–		

M.P. = metacarpo-phalangeal joint
I.P. = interphalangeal joint
+ = found
– = not found

Case Reports

Case 1, a male aged 64, was admitted to another hospital because of generalized pains of recent onset.

Clinical Findings.—Shortly after admission he was seen to develop painful swellings of the wrists, hands, and feet; and during the next 6 months the ankles, elbows, shoulders, and knees became involved despite twenty injections of gold and an unspecified amount of DOCA and ascorbic acid; 11 months after the onset, he was examined in the Out-Patient Department of the Manchester Rheumatism Centre and found to have pale, atrophic skin and subcutaneous nodules on both elbows and ischial tuberosities; the joints of the hands, feet, wrists, knees, and elbows were swollen, painful, and limited in movement; there was ulnar deviation of the hands, flexion deformity of the knees, and slight subluxation of both shoulders. General examination revealed no abnormality apart from slight dullness and diminished movement over the left lower lobe. The blood pressure was 140/80; urine normal; erythrocyte sedimentation rate (Westergren) 81 mm./hr. A month later, on admission to the Centre's Ward, the condition of the joints and other signs of rheumatoid arthritis remained unchanged but there was a mild pyrexia up to 101° F. and a left pleural effusion in which 70 per cent. of the cells were polymorphs, though it was sterile on culture. Radiographs of the chest, both at this time and later when the effusion had subsided, revealed no underlying pulmonary lesion. Radiographs of the hands, knees, hips, and shoulders showed advanced bilaterally symmetrical destructive arthritis of the rheumatoid type. The erythrocyte sedimentation rate was now 90 mm./hr; haemoglobin 70 per cent.; white cell count 15,000/c.mm.; D.A.T. positive. Repeated tests of the urine for albumin and sugar were negative. Intravenous iron was given but discontinued after nine injections because of some attendant distress. The pyrexia persisted, though apparently partially controlled by aureomycin; there was no sign of local sepsis and blood cultures were sterile. The patient's general condition steadily deteriorated and death occurred 3 weeks after admission and some 12 months after the onset of the illness, acute abdominal pain and tenderness being present in the last few days.

Pathological Findings

Macroscopic.—There was wasting of subcutaneous fat and limb muscles. Typical subcutaneous rheumatoid nodules were found in the elbow region. All the limb joints showed some degree of subluxation and the joint capsules were thin and atrophic. The right knee, right shoulder, and left hip joint contained much yellowish friable debris, partly lying free and partly attached to the slightly thickened but generally smooth synovial membrane; the biceps psoas and semimembranous bursae were distended with similar material. Both trochanteric bursae were thickened and the red lining-membrane was mottled with irregular yellowish patches.

The heart (210 g.) and pericardial sac were normal. There was a left pleural effusion, and a thick shaggy fibrinous exudate covered the lower lobe of the left lung (700 g.). On section, a terminal broncho-pneumonia was found in both lungs. Scattered throughout the small intestine were numerous ulcers (0·5-1·0 cm.) with associated recent peritoneal fibrinous exudate; a paraduodenal abscess containing yellow pus communicated with a mucosal ulcer. A solitary deep chronic ulcer was found in the pyloric region of the stomach. The adrenals together weighed 20 g. and appeared normal, as did the spleen, pancreas, and kidneys. The liver (1,240 g.) contained occasional friable bluish areas about 0·5 cm. in diameter. There was slight dilatation of the lateral ventricles. In the region of the optic chiasma there was a localized gelatinous exudate, but the meninges were otherwise normal.

Microscopic

Viscera.—Polyarteritis nodosa was found in the small arteries of the kidneys, pancreas (Fig. 1), stomach, and small intestine, and in the bronchial arteries at the hilum of the left lung. These lesions were all in the acute or early subacute phase. Renal and splenic parenchyma were not notably abnormal. There was an area of pleomorphic cellular infiltration at the base of the posterior mitral cusp, but evidence of either rheumatic carditis or Libman-Sachs endocarditis was not seen. Occasional areas of haemorrhagic necrosis were present in the liver. The left pleura and overlying exudate presented no unusual features. In the region of the optic chiasma the pia-arachnoid contained an indeterminate inflammatory exudate infiltrated with lymphocytes.

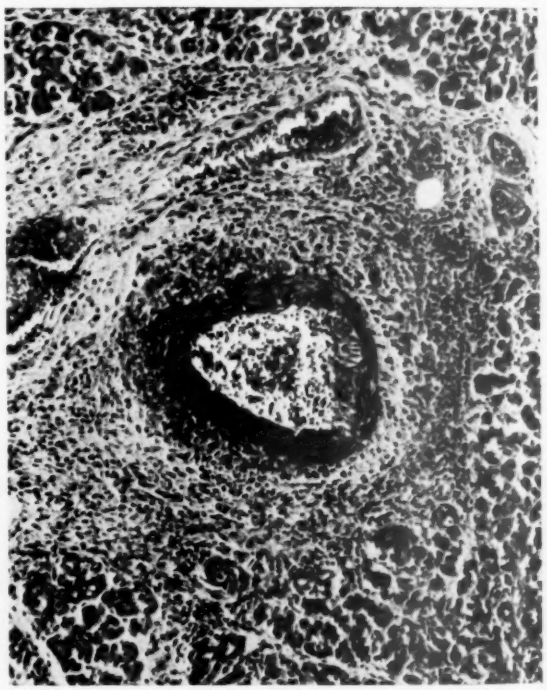


Fig. 1.—Case 1, acute polyarteritis nodosa in pancreas. Haemalum and eosin. × 115.

Articular Tissues.—The fibrous wall of the trochanteric and bicipital bursae contained areas of fibrinoid. In the surrounding muscle and connective tissue occasional acute lesions of polyarteritis nodosa were seen. The wrist joint was partially ankylosed, and subchondral erosions were numerous in the carpal bones. Some of the eroded areas were filled with necrotic debris and lined in parts with oedematous connective tissue scantily infiltrated with lymphocytes; others contained vascular fibrous pannus. There was acute arteritis in the periosteal tissues, but not in the joint capsule. Early pannus erosion of cartilage was found in the knee joint, where arteritis was present in the joint capsule and periarticular tissues.

In the metacarpo-phalangeal joint characteristic erosions by fibrous pannus infiltrated with lymphocytes and plasma cells were evident, but the synovium generally was only moderately infiltrated with lymphocytes. In the synovial recesses fibrinous masses were conspicuous. Acute polyarteritis was present in the peri-articular muscles and periosteal tissues, but not in the joint capsule or synovium (Fig. 2).

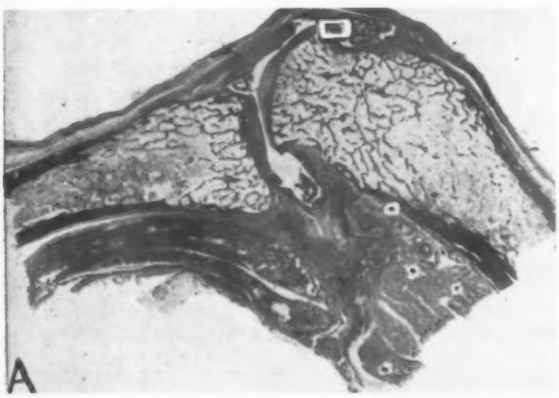
The articular histology suggested that a severe rheumatoid process had become relatively quiescent some time before death.

Summary.—Clinically, this patient had a rapidly progressive rheumatoid arthritis of some 12 months' duration. The occurrence of a sterile pleural effusion and failure to respond to bed rest and other supportive measures were the principal clinical features in the last few weeks of the illness, though terminally acute abdominal symptoms developed.

Histological studies revealed polyarteritis nodosa in various internal organs and in the peri-articular tissues, particularly the flexor muscle groups. Though some of the features of rheumatoid arthritis, such as villous synovial hypertrophy and dense inflammatory infiltrates were absent, typical rheumatoid erosions of articular cartilage and subchondral bone were conspicuous. The persistence of joint pain and tenderness in the final stages of the illness, when the arthritis was judged histologically to be relatively inactive, may be explained by the late occurrence of arteritis in the peri-articular tissues and outer parts of the joint capsule.

Case 2, a female aged 64, attended the Infirmary complaining of pains in the joints of 6 months' duration.

Clinical Findings.—Examination revealed tender swelling of the joints of the fingers, wrists, ankles, and knees, and some painful limitation of movement of the shoulders and cervical spine. There was some deafness in the



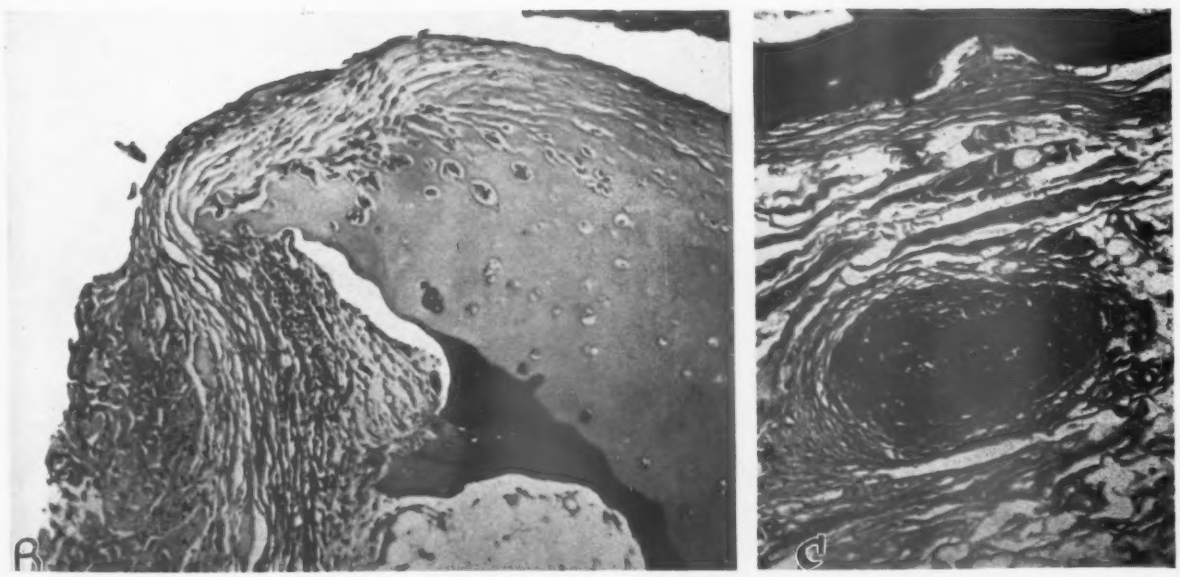


Fig. 2.—Case 1
(A) Metacarpo-phalangeal joint. White spots indicate sites of arterial lesions.
(B) Outlined area enlarged to show typical rheumatoid erosion of cartilage and subchondral bone.
(C) Acute polyarteritis nodosa in a juxta-articular vessel.

right ear and a slight discharge from a frontal sinus that had been operated on 30 years previously, but otherwise no abnormality was detected on general examination. A diagnosis of early rheumatoid arthritis was made, and 3 months' physiotherapy was followed by a course of gold injections. These were terminated after a further 4 months because of skin irritation which rapidly subsided. A white cell count taken some time later was 9,200/c.mm. and the haemoglobin was 82 per cent.

The arthritis continued to be active and 4 months after cessation of gold therapy and following a rapid deterioration in her general condition she attended hospital again. There was a mild pyrexia (101° F.), obvious loss in weight, and severe polyarthritis. The blood pressure was 110/60, and white cell count 10,000/c.mm. A small scirrhous carcinoma was found in the left breast and radical mastectomy was performed the following week. After operation the wound broke down and there was a persistent pyrexia which was unaffected by penicillin; 7 weeks after the operation a peripheral neuritis developed and 5 weeks later, following a steady deterioration in the general condition, the patient died. The total duration of the illness had been 20 months.

Pathological Findings

Macroscopic.—There was severe general wasting and large sores over the sacrum. Apart from a slight spindling of the fingers there was no obvious joint deformity. There was a recent mild pericarditis and the flabby myocardium contained occasional small haemorrhagic foci; no valvular or endocardial abnormality was found in the heart (260 g.). The loops of the small intestine were bound by numerous focal adhesions and there was superficial ulceration of the mucosal surface. The liver (1,140 g.) contained several small haemorrhagic areas. The spleen, pancreas, kidneys, adrenals, brain, stomach, and large intestine were apparently normal.

Post-mortem x rays of the right index finger and cervical interfacetal joints revealed slight reduction in joint space and several small erosions of rheumatoid type.

Microscopic

Viscera.—There was a mild non-specific fibrinous pericarditis, but no definite evidence of rheumatic heart disease. Polyarteritis nodosa, mainly in the subacute or healed phase, was found in the myocardium, limb muscles, liver, kidneys, periadrenal fat, serous coat of small intestine, and sciatic and median nerves (Figs 3 and 4). Renal and splenic parenchyma presented no definite abnormality. The pituitary contained rare groups of polar bigranulate cells (Pearse, 1953).

Articular Tissues.—The joints of the right index finger and one knee joint were examined histologically and typical rheumatoid erosions of the marginal articular cartilage and subchondral bone were found in them all (Fig. 5, opposite); the synovial tissue and pannus formations were moderately infiltrated with lymphocytes and plasma cells. The arthritic process was judged to be relatively mild in comparison with Case 1. Subacute and healed lesions of polyarteritis were present in the periarticular muscle and joint capsule of the metacarpophalangeal joint and in the intercondylar fossa of the right knee joint; but no vascular lesions were detected in the proximal and distal interphalangeal joints, where the rheumatoid process was equally advanced.

Summary.—For some 17 months a female aged 64 presented the typical features of a rheumatoid arthritis of

Fig. 3.—Case 2, fibrinoid change in an artery in voluntary muscle. Haemalum and eosin. × 115.

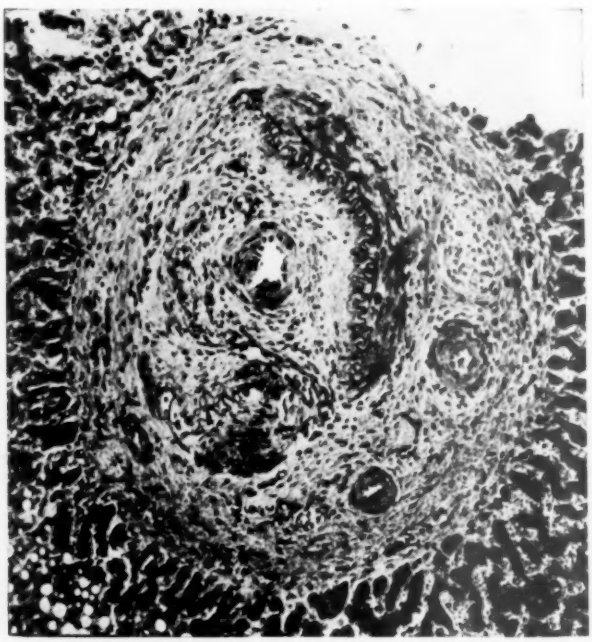


Fig. 4.—Case 2, healed polyarteritis nodosa in liver. A segment of the wall is replaced by fibrous tissue and there is almost complete fibrous occlusion of the lumen. Masson-Goldner. × 115.

Fig. 5.—Case 2, metacarpo-phalangeal joint, showing marginal erosion of articular cartilage and subchondral bone, lymphocytic infiltration, and fibrosis of subchondral marrow. Haemalum and eosin. × 120.

moderate severity. She died 3 months after a radical mastectomy; and the occurrence of a peripheral neuritis 5 weeks before death was the first sign of polyarteritis nodosa. Subacute and healed lesions of polyarteritis were found in the peripheral nerves and various internal organs, and in the peri-articular vessels of most but not all of the affected joints in which changes typical of rheumatoid arthritis of a severity compatible with the clinical observations were present. Thus the evidence both clinical and pathological strongly suggests that the arteritis was superimposed on an established rheumatoid process.

Case 3, a male aged 62, developed pain in the left shoulder early in 1950. This was followed, in a few weeks, by painful swelling of the joints of the hands and feet. Within 6 months the knees, hips, and cervical spine became involved and he had lost a stone in weight. A course of gold injections was given, and by April, 1951, he had returned to work, the only residual disability being some stiffness of the left hand. Five months later the symptoms recurred and he was again treated with gold, but after six injections the treatment was discontinued owing to an attack of coronary thrombosis from which he made a good recovery; he had had a similar episode 10 years previously. During the next 9 months the arthritis became gradually worse and he was admitted to the Infirmary in June, 1952.

Clinical Findings.—On examination the hands were cold and moist, and typical subcutaneous nodules were present over the elbows, scapulae, sacrum, and occiput, and in the fingers. There was painful swelling of the joints of the hands and feet, and painful limitation of movement in the elbows, hips, shoulders, and cervical spine. The only abnormal sign on general examination was a slight sensory impairment in the left leg and both feet. Changes indicative of old coronary infarction were present in the electrocardiograph. *X* rays showed extensive articular erosions of rheumatoid type. The blood pressure was 160/85-100; urine normal; haemoglobin 80 per cent.; albumin-globulin ratio 0·8; D.A.T. positive.

One week after admission another coronary attack occurred for which anticoagulant therapy was given for 3 weeks. At this time ulceration occurred over the subcutaneous nodules, and antibiotic therapy was instituted to control secondary infection. Blood cultures were sterile and there was never a severe pyrexia; the highest white cell count was 28,100/c.mm., and the blood urea reached 76 mg. per cent. The general condition steadily deteriorated and a month after admission he had another attack of severe retrosternal pain and dyspnoea. Death occurred 3 weeks later, 1,100 mg. cortisone having been given in the last 7 days.

Pathological Findings

Macroscopic.—There was general wasting and ulcers were present over most pressure points. The olecranon bursae were enlarged and thickened, and typical fibrinoid nodules were found in the subcutaneous tissue along the ulnar border. There was ulnar deviation of the hands and a flexion deformity of the knees. The heart (550 g.) was enlarged and there was fibrinous pericarditis; the posterior wall of the left ventricle contained an infarct and the proximal 2 in. of the right coronary artery were completely occluded by firm thrombus. Both coronary arteries were severely atheromatous. Two of the aortic valves were firmly adherent but otherwise the heart valves and endocardium were normal. There was pneumonic consolidation of the lower zones of both lungs which were adherent posteriorly. A deep ulcer (1 cm. diam.) was present in the first part of the duodenum and smaller superficial ulcers were scattered throughout the small and large intestine. There was some distortion of the cortical pattern in both kidneys, and the right contained an old infarct. Two red infarcts were present in the spleen (90 g.) which was otherwise normal. The portal tracts in the left lobe of the liver (1,150 g.) were unduly prominent.

Microscopic

Viscera.—Many of the larger renal arteries showed focal destruction of elastic and muscle layers and partial or complete fibrous occlusion of the lumen (Fig. 6, overleaf).

Some of the smaller vessels resembled endarteritis

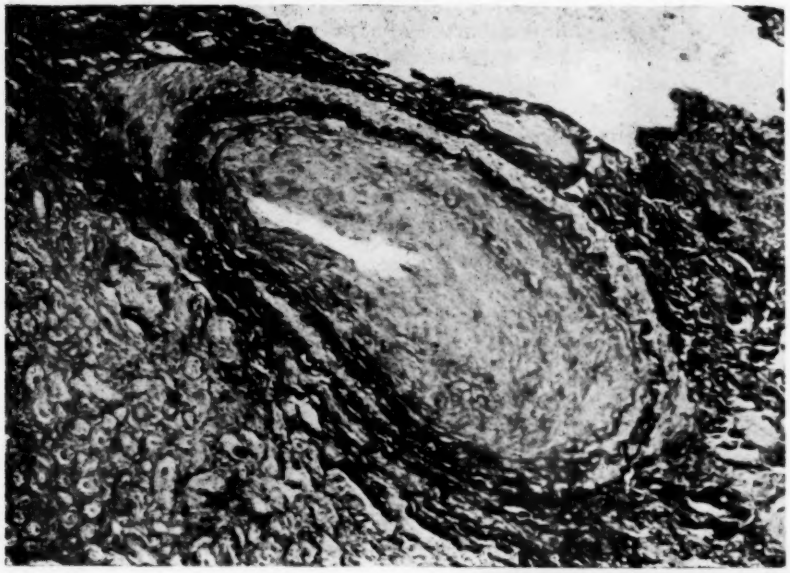


Fig. 6.—Case 3, renal artery showing focal loss of elastic and muscle coats with associated perivascular fibrosis. Gross intimal fibrosis.
Weigert's elastic and Van Gieson. × 80.

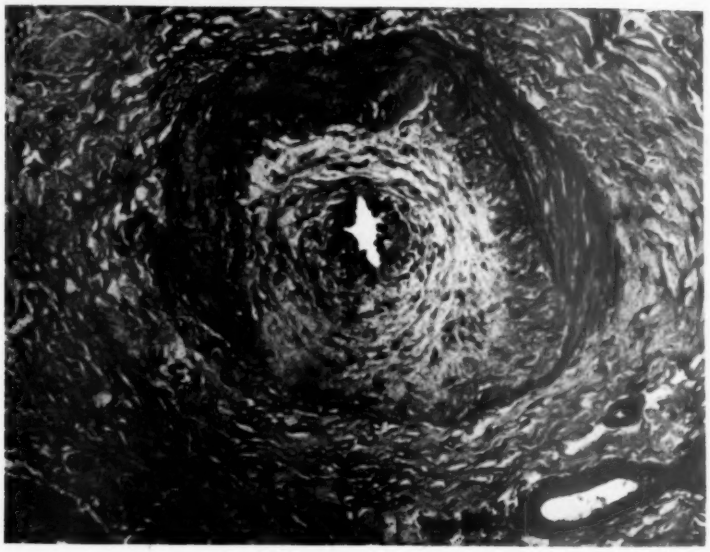


Fig. 7.—Case 3, liver, showing healed polyarteritis nodosa. Part of wall completely destroyed, with severe arterial and periarterial fibrosis.
Masson-Goldner. × 170.

fibrosa, but clinically there was no evidence of hypertension and hypertensive glomerular changes were absent. Subacute or healed lesions of polyarteritis nodosa were seen in the portal tracts (Fig. 7), spleen, pancreas, and duodenum. In the kidneys the lesions were associated with groups of fibrosed glomeruli and atrophic tubules but otherwise the renal parenchyma was not remarkable. In addition to myocardial fibrosis, there were recent and old infarcts in the left ventricle, but no evidence of polyarteritis nodosa, the coronary arteries showing only severe atheroma. Where secondary infection was minimal or absent, it was clear that the skin ulcers had developed by subepidermal extension of subcutaneous fibrinoid with consequent sloughing of the epidermis. Rare groups of polar bigranulate cells and occasional Crooke-Russell cells were present in the pituitary.

Articular Tissues.—Typical rheumatoid marginal articular erosions were found in the sternoclavicular joints, the disks of which contained areas of fibrinoid change; arteritis was not encountered in the joint capsule or peri-articular tissues in several sections. Similarly there was a moderately severe destructive arthritis in the metacarpo-phalangeal joint and terminal interphalangeal joint of the right index finger without articular polyarteritis nodosa. The anterior and posterior atlanto-axial joints were largely replaced by pannus at various stages of maturity, and remnants of synovial tissue presented typical rheumatoid changes; areas of fibrinoid were seen in the apical and alar ligaments (Figs 8 and 9, opposite).

No polyarteritis was found in sections of this region. All of three cervical interfacetal joints showed typical

Fig. 8.—Case 3, atlanto-axial joints:
(*a*) anterior arch of atlas covered by pannus,
(*b*) odontoid process showing erosion of apex.
Alar and apical ligaments contain dark areas of fibrinoid.

Fig. 9.—Case 3, enlargement of outlined area in Fig. 8 to show replacement of articular cartilage down to bone by pannus. Masson-Goldner. × 170.

marginal rheumatoid erosions; though vascular lesions were found occasionally in the intervertebral foramina, the vessels in the joint capsules were not involved.

Summary.—A 62-year-old male, who had suffered from severe rheumatoid arthritis for over 2 years, died of atheromatous coronary disease. The only unusual clinical sign was the occurrence of sensory impairment in the lower limbs late in the course of the illness. Histological studies confirmed the diagnosis of rheumatoid arthritis and also disclosed healed polyarteritis nodosa of various internal organs; the articular vessels, however, were not involved in most of the affected joints, so that there can be little doubt that the arthritis was pathogenetically independent of articular polyarteritis nodosa. It is difficult to date the onset of the arteritis, though this is the probable explanation of the sensory impairment noted 7 weeks before death.

Case 4, a male aged 50, was admitted to the Manchester Rheumatism Centre because of severe polyarthritis. His illness had started 13 years previously with painful swelling of the joints of the feet; 4 years after the onset, the hands, knees, and cervical spine became involved, and subcutaneous nodules appeared on the elbows. During the succeeding 9 years all the affected joints became increasingly deformed and though there was no great constitutional disability the patient had lost 4 stones in weight.

Clinical Findings.—The skin was found to be atrophic and the hands were cold, moist, and cyanotic. Typical rheumatoid nodules were present in the flexor tendons of the hands and in the elbow and sacral regions. The joints were deformed, tender, and swollen. General examination revealed no abnormality. The blood pressure was 160/95; urine normal (and remained so throughout); E.S.R. (Westergren) 90 mm./hr; D.A.T. positive; haemoglobin 82 per cent.; white cell counts 3,500 and 5,000/c.mm.; lupus erythematosus cells looked for but not found; albumin/globulin ratio 0·7.

X rays showed gross rheumatoid changes in hands and feet, lateral subluxation of the atlas, and normal sacro-iliac joints. A course of gold injections was started and 2 weeks after admission the patient was transferred to the Devonshire Hospital, Buxton, where a collar was applied to the neck. At this time the patient was confined to bed because of general malaise associated with slight buccal ulceration; white cell count 5,600/c.mm.; temperature normal apart from occasional rises to 100° F. He collapsed and died suddenly 11 days after admission.

Pathological Findings

Macroscopic.—There was gross deformity of the limb joints and typical subcutaneous nodules over both elbows. Both lungs were severely congested, but the pleural cavities were normal. There was a shaggy pericarditis and an abundant haemorrhagic pericardial effusion. The coronary arteries were patent but atheromatous, and there was severe myocardial fibrosis. The valves and endocardium were normal. Small (1-3 mm.) nodules were scattered throughout the liver which was adherent to the

diaphragm. There was an old adherent perisplenitis but otherwise the spleen appeared normal. The brain and cervical cord were not remarkable apart from a small haemorrhagic lesion in the membranes in the region of the second cervical vertebra.

Microscopic

Viscera.—Subacute or healed lesions of polyarteritis nodosa were readily found in the pancreas, liver, spleen, kidneys, stomach, and intestine (Fig. 10), and in the auricular and ventricular myocardium. There was no evidence of rheumatic heart disease, and the pericarditis presented no unusual features. There was some peri-arteriolar hyalinosis in the spleen, but the renal, hepatic, and splenic parenchyma were not remarkable. No definite abnormality was seen in the pituitary.

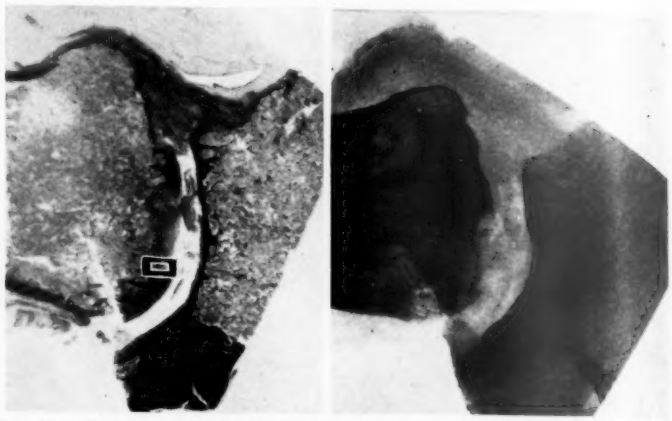


Fig. 11.—Case 4, *x*-ray and corresponding section of sterno-clavicular joint showing destruction of disk and replacement of cartilage and bone by fibrous pannus.

Fig. 10.—Case 4, polyarteritis nodosa in small artery in small intestine.

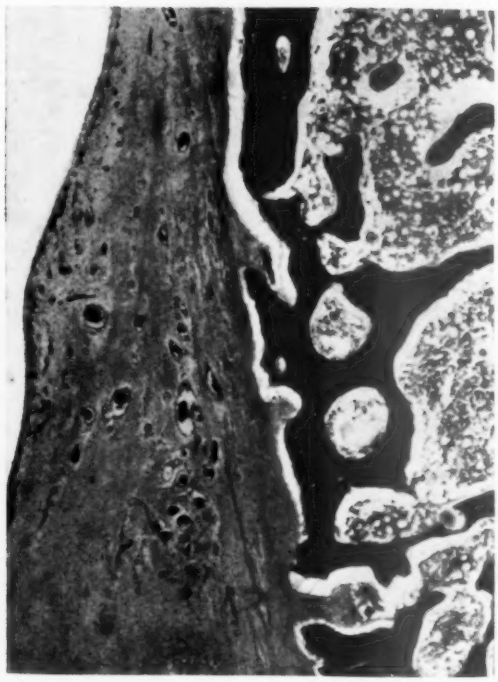


Fig. 12.—Case 4, enlargement of area outlined in Fig. 11 to show vascular fibrous pannus covering partly eroded bone at articulating surface of clavicle.
Haemalum and eosin. × 48.

Articular Tissues.—The sternoclavicular joint, wrist joint, and carpus all showed a severe destructive but quiescent arthritis of rheumatoid type with some secondary osteo-arthritis (Figs 11 and 12). Polyarteritis nodosa was present in the capsule and peri-articular tissues of the wrist and carpal joints, but no arterial lesions were detected in several sections of the sterno-clavicular joint. Vascular lesions were also found in the muscles and intervertebral foramina in the vicinity of the cervical interfacetal joints in which minor rheumatoid changes were evident.

Summary.—Clinically there was no reason to suspect that the patient was suffering from anything but advanced rheumatoid arthritis of some 13 years' duration. Death was probably due to haemorrhagic pericarditis and myocardial failure associated with myocardial polyarteritis nodosa; arteritis was also present in various other organs. Histologically the joint changes were typical of advanced rheumatoid arthritis of long duration.

Case 5, a female aged 53, was admitted to the Infirmary complaining of cough, breathlessness, and loss of weight of 2 months' duration.

Clinical Findings.—Investigation revealed a mild pyrexia, a sterile right-sided pleural effusion, mitral stenosis, a mild anaemia (haemoglobin 76 per cent.), a white cell count of 9,200/c.mm., and sterile blood cultures. The pyrexia gradually subsided following penicillin therapy, but in spite of comprehensive studies no satisfactory explanation of the pleural effusion was found. The pleural effusion was considerably reduced in size 6 weeks after admission, and the patient was discharged. She was subsequently seen at intervals as an out-patient, but after 3 months was readmitted because of increasing breathlessness, fatigue, and pain and stiffness in the arms, legs, and back. There was painful limitation of movement in the hands, feet, wrists, ankles, shoulders, and spine. X rays of the hands showed juxta-articular porosis but no bony erosions. Weight loss was obvious, but the temperature, pulse, and blood pressure were normal. Salicylates were given, but the patient remained unwell, and shortly after admission developed bouts of pyrexia and auricular fibrillation which was controlled with digitalis; the blood cultures were sterile. A Wasserman reaction at this time was positive but no other evidence of syphilis was found; erythrocyte sedimentation rate 43 mm./hr; urine contained albumin, a few red and white blood cells, and granular casts; blood urea 58 mg./100 ml.; haemoglobin 64 per cent., and persistent polymorphonuclear leucocytosis, the count rising as high as 21,600 c.mm.; albumin/globulin ratio 0·9; tests for amyloid and lupus cells and D.A.T. negative.

A diagnosis of polyarteritis nodosa was made and 100 mg. cortisone daily was given for 23 days, being stabilized after a 12-day interval at 25 mg. on alternate days. From the start of cortisone therapy there was a considerable and steady improvement in her general condition and when she was discharged some 3½ months after admission the joint symptoms had disappeared.

However, 3 weeks after discharge and whilst still taking cortisone, she was readmitted as an emergency because of increasing oedema, cough, breathlessness, and lassitude. On examination there was pyrexia, pulmonary oedema, ascites, and oedema of the ankle, but no distension of the neck veins; blood pressure 106/56; blood urea 58 mg./100 ml.; white cell count 19,800/c.mm. (92 per cent. polymorphs). There were no symptoms or signs of joint disease. Death occurred 2 days after admission.

Pathological Findings

Macroscopic.—The skin, subcutaneous tissue, and joints presented no definite abnormality. The heart weighed 470 g.; there was recent pericarditis, an old stenosis of the mitral valve, and slight aortic sclerosis, but no recent endocarditis. Both lungs were bound down by easily separable adhesions. There was a rubbery consolidation of the mid-zone of the left lung (740 g.), the cut surface being moist and purple in colour; in the surrounding areas there was congestion and oedema only. The right lung showed congestion and oedema. The peritoneal cavity contained about 0·5 l. sero-fibrinous fluid. There was passive congestion of the liver (1,350 g.) and spleen (350 g.) and an adherent perisplenitis. The kidneys were not enlarged, but occasional haemorrhagic or scarred areas were found in the cortex. The brain was normal.

Microscopic

Viscera.—Acute and subacute polyarteritis nodosa was found in the liver, kidneys (Fig. 13), intestine, pancreas, adrenals, and omentum. The renal lesions were associated with areas of haemorrhage and fibrosis but otherwise the kidney was not remarkable. In the area of consolidation in the left lung, the alveoli were lined by swollen endothelial cells and contained masses of fibrinous material, some of which were being organized; the alveolar septa were thickened partly by oedema and partly by fibrous tissue. The appearances were similar to those often described as "rheumatic pneumonia". In the pituitary there was an obvious reduction in the staining of the basophils with the periodic acid-Schiff method; Crooke-Russell cells were easily found, but polar bigranulate cells were rare.

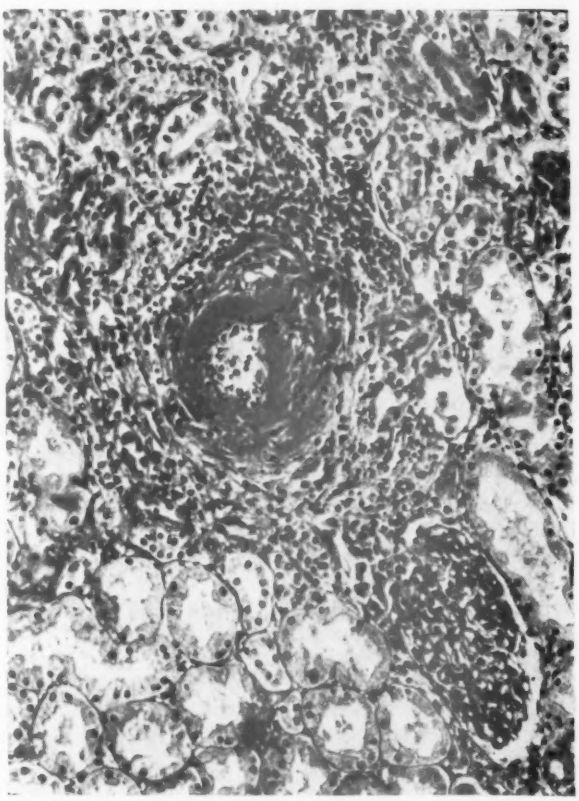


Fig. 13.—Case 5, polyarteritis nodosa in small renal artery. Haemalum and eosin. × 150.

Articular Tissues.—The right metacarpo-phalangeal joint and first interphalangeal joint were examined. Both showed unmistakable rheumatoid erosions of the marginal articular cartilage in an inactive stage (Fig. 14). Numerous sections of these parts were scrutinized without finding polyarteritis nodosa.

Fig. 14.—Case 5, metacarpo-phalangeal joint showing marginal erosion of articular cartilage and subchondral bone by pannus in a quiescent phase. Haemalum and eosin. × 75.

Summary.—The combination of rheumatic heart disease, unexplained pleural effusion and leucocytosis, weight loss, mild arthropathy, and a urine containing albumin, red cells, and casts, suggested polyarteritis nodosa in life, and this was confirmed at necropsy. Unlike the previous cases the arthropathy was never a feature of major clinical importance. Nevertheless the joint changes were histologically typical of the rheumatoid process and occurred in the absence of articular polyarteritis nodosa.

This case clearly illustrates that, in patients apparently suffering primarily from polyarteritis nodosa, a typical rheumatoid arthritis may occur, the joint changes being independent of arterial lesions and analogous to the non-specific pericarditis commonly found in this disease.

Discussion

The diagnosis of rheumatoid arthritis in Cases 1 to 4 was clearly justified on clinical, radiological, and serological grounds; moreover, until shortly before death, there was no indication of the fatal outcome. The final stages were characterized mainly by a steady deterioration in the general condition. Only in Case 2 were there definite signs of polyarteritis nodosa in life, but in Cases 1, 3, and 4 there were terminal visceral or neurological episodes which in retrospect could be interpreted as clinical evidence of a disseminated arteritis. In three of the cases polyarteritis nodosa was probably a major contributory cause of death; the remaining patient (Case 3) died of atheromatous coronary thrombosis, and in this case the lesions of periarteritis nodosa had healed. In Case 1 the arterial lesions were probably of recent origin, being in the acute phase and contemporaneous (an unusual finding in polyarteritis nodosa), whereas the arthritis had been present for nearly a year; and in Cases 2 and 3 suggestive signs of disseminated arteritis were first detected shortly before death. In Case 4, progressive rheumatoid arthritis had been present for 13 years without unusual symptoms or signs, until death occurred unexpectedly from heart failure.

Histologically, there was a typical rheumatoid process in the joints; in addition, arteries in the peri-articular tissues were commonly involved by polyarteritis nodosa, but the smaller capsular and synovial vessels were unaffected in most instances; nor did the synovial tissues contain focal granulomatous lesions such as may be encountered in polyarteritis nodosa and have been ascribed to capillary involvement (Ball and Davson, 1952). And in all but Case 1 there were occasional joints with rheumatoid changes but without peri-articular arteritis. Thus, in Cases 1 to 4, clinical and histological evidence favours a double diagnosis, in the sense that the arteritis was superimposed on a true rheumatoid arthritis. It is possible, however, that the peri-articular arteritis was responsible, at least in part, for the persistent joint symptoms in those instances in which the arthritis appeared to be relatively inactive histologically.

The studies of Sokoloff and others (1951) and of Cruickshank (1954) indicate that in certain rare cases of rheumatoid arthritis an arteritis may occur, in which mural necrosis or fibrosis are inconspicuous, and which may therefore be reasonably regarded as different from polyarteritis nodosa. It is noteworthy, however, that among the group of eleven cases described by Cruickshank (1954) as having "rheumatoid arteritis", a fairly wide range of appearances were encountered in the affected vessels; and in two (Cases 8 and 17) the lesions, though remarkably similar to classical acute polyarteritis nodosa, were distinguished from it because there was neither

aneurysm formation nor thrombosis and because the lesions were not widely disseminated in the viscera. Both these criteria seem open to question, for it is generally acknowledged that many cases of polyarteritis nodosa do not show aneurysm formation, and the distribution and frequency of the lesions are well known to vary widely from case to case. There is an interesting parallel here with the arteritis found in some cases of rheumatic fever: this was regarded by Von Glahn and Pappenheimer (1926) as specific to this syndrome, for reasons similar to those advanced by Cruickshank regarding rheumatoid arteritis. But, in the cases of rheumatic fever described by Friedberg and Gross (1934), the arterial lesions were considered to be typical of polyarteritis nodosa, and it was suggested that the differences between these authors' cases and those of Von Glahn and Pappenheimer might be quantitative rather than qualitative. Similar difficulties may apparently also arise in the interpretation of the arterial lesions that occur in some cases of disseminated lupus erythematosus (Bauer and others, 1952). The available evidence suggests that the distribution, frequency, and morphology of arterial lesions in rheumatoid arthritis are variable, ranging from a mild indeterminate arteritis to classical polyarteritis nodosa.

Although the various syndromes comprising the collagen diseases are usually fairly well defined clinically and pathologically, cases showing features of more than one syndrome are frequently encountered; and arteritis more or less typical of polyarteritis nodosa has been found in association with rheumatic fever, disseminated lupus erythematosus, scleroderma, and dermatomyositis (Friedberg and Gross, 1934; Banks, 1941; Klemperer and others, 1941; Bevans, 1945; Klemperer, 1948; Bauer and others, 1952). It would appear that the same can be said of rheumatoid arthritis, which is, however, a relatively common disease. Nevertheless, there is suggestive evidence that the association of rheumatoid arthritis and polyarteritis nodosa is more than coincidental. Thus, the incidence of rheumatoid arthritis in the general population has been variously estimated at 1 per cent. (Blécourt, 1953) and 2·4 per cent. (Kellgren and others, 1953), whereas its incidence in polyarteritis nodosa is probably 8 per cent. according to Rose (1953).

The implication is that, in the presence of any of the syndromes mentioned above, there is an increased susceptibility to arterial disease of the polyarteritis nodosa type. But, since only a small proportion of patients with rheumatoid arthritis become hospital in-patients and few of these die, it is obvious that polyarteritis is a rare complication of this syndrome and one likely to be seen mainly in hospital practice. It is clinically important, not because of its frequency, but because it may be fatal and may not readily be recognized as such when superimposed upon the picture of severe rheumatoid arthritis.

The personal study of a considerable amount of biopsy material in rheumatoid arthritis confirms previous opinions that polyarteritis nodosa is a very rare feature of rheumatoid pathology; and the appearance of vascular lesions in the present cases is presumably dependent on pathogenetic factors not usually operative in this form of polyarthritis. Conversely, histological evidence of a rheumatoid process (in the absence of articular arteritis) may be found in cases of polyarteritis nodosa in which joint disability is not a presenting feature (Case 5).

Cases 1 to 4 were carefully reviewed without discovering any common factor which could be regarded as causally significant in relation to the arteritis. There was, for instance, no evidence clinically of a hypersensitivity state; and visceral granulomata, which sometimes accompany polyarteritis nodosa (Wegener, 1939) and to which Zeek and others (1952) attach an allergic significance, were not encountered in the present cases. However, McManus and Hornsby (1951) have recently described necrotizing arteritis and granulomatous glomerulo-nephritis following polyarthritis, and I have seen this Wegener type of polyarteritis nodosa develop in a typical case of ankylosing spondylitis with peripheral joint involvement.

The occurrence of disseminated arteritis in patients under treatment with cortisone has aroused considerable interest. According to Slocumb (1953), attempts to withdraw cortisone therapy may be attended by a "panmesenchymal and panangiitic reaction" which carries all the risks of polyarteritis nodosa or acute disseminated lupus erythematosus; and he makes the further interesting statement that among various patients treated with cortisone, a panangiitic reaction was seen only in those with rheumatoid arthritis. Two of 33 cases of rheumatoid arthritis described by Levin and others (1953) died of polyarteritis nodosa which developed after withdrawal of cortisone; but these workers point out, as do West and Newns (1953), that this complication may also begin during the period of administration of the hormone. It is evident from all these reports that before being given cortisone therapy the cases developing arteritis were not distinguishable from those that did not; and it has been suggested that the treatment was at least partly responsible for the development of the arteritis. It is, however, clear that a similar sequence of events may arise in the absence of ACTH or cortisone therapy.

Summary

Clinical and necropsy findings are presented in five cases, illustrating the association of rheumatoid arthritis and polyarteritis nodosa.

In four of these, disseminated arteritis apparently complicated an established and typical rheumatoid process, the pathogenesis of the arthritis being essentially independent of the arterial lesions. In one case the arteritis was an incidental finding, in the others it was a major contributory cause of death. Only one of the four cases had received cortisone; none had received ACTH.

In the fifth case a short arthritic episode occurred in an illness diagnosed clinically and histologically as polyarteritis nodosa; at necropsy the joints showed typical rheumatoid changes in the absence of articular arteritis.

It is suggested that, though polyarteritis nodosa is a rare complication of rheumatoid arthritis, the association of these two conditions is more than coincidental. The available evidence suggests that the distribution, frequency, and morphology of arterial lesions in rheumatoid arthritis are variable, ranging from a mild indeterminate arteritis to classical polyarteritis nodosa.

I wish to thank Professors S. L. Baker and J. H. Kellgren for assistance with the manuscript. I am also indebted to Professor J. H. Kellgren, Professor R. Platt, Dr. W. Brockbank, and Mr. W. F. Nicholson for permission to use the clinical records of Cases 1, 3, and 4, Case 5, and Case 2 respectively.

REFERENCES

Baggenstoss, A. H., and Rosenberg, E. F. (1943). *Arch. Path.* (*Chicago*), **35**, 503.
Ball, J. (1952). *Annals of the Rheumatic Diseases*, **11**, 97.
——, and Davson, J. (1949). *J. Path. Bact.*, **61**, 569.
Banks, B. M. (1941). *New Engl. J. Med.*, **225**, 433.
Bauer, W., Giansiracusa, J. E., and Kulka, J. P. (1952). *In* "Rheumatic Diseases", based on Proc. VII Int. Congr. Rheum. Dis., 1949, p. 391. Saunders, London.
Bennett, G. A. (1943). *Ann. intern. Med.*, **19**, 111.
——, Zeller, J. W., and Bauer, W. (1940). *Arch. Path.* (*Chicago*), **30**, 70.
Bevans, M. (1945). *Amer. J. Path.*, **21**, 25.
Blécourt, J. J. de (1953). *Rev. Rhum.*, **20**, Numéro Special, p. 105.
Collins, D. H. (1949). "The Pathology of Articular and Spinal Disease", p. 207. Arnold, London.
Cruickshank, B. (1952). *J. Path. Bact.*, **64**, 21.
—— (1954). *Annals of the Rheumatic Diseases*, **13**, 136.
Dawson, M. H. (1940). *Ann. intern. Med.*, **13**, 1837.
Fingerman, D. L., and Andrus, F. C. (1943). *Annals of the Rheumatic Diseases*, **3**, 168.
Friedberg, C. K., and Gross, L. (1934). *Arch. intern. Med.*, **54**, 170.
Friedman, H. H., Schwartz, S., Trubek, M., and Steinbrocker, O. (1953). *Ibid.*, **38**, 732.
Gross, L., Antopol, W., and Sacks, B. (1930). *Arch. Path.* (*Chicago*), **10**, 840.
Jones, G. M. (1942). *Ann. intern. Med.*, **16**, 920.
Kellgren, J. H., Lawrence, J. S., and Aitken-Swan, J. (1953). *Annals of the Rheumatic Diseases*, **12**, 5.
Klemperer, P. (1948). *Ann. intern. Med.*, **28**, 1.
——, Pollack, A. D., and Baehr, G. (1941). *Arch. Path.* (*Chicago*), **32**, 569.
Levin, M. H., Rivo, J. B., Scott, W., Figueroa, W. G., Fred, L., and Barrett, T. F. (1952). *Amer. J. Med.*, **14**, 265.
Lowman, E. W. (1952). *Annals of the Rheumatic Diseases*, **11**, 146.
McManus, J. F. A., and Hornsby, A. T. (1951). *Arch. Path.* (*Chicago*), **52**, 84.
Nyström, G. (1953). *Ann. Med. intern. Fenn.*, **42**, 52.
Pearse, A. G. E. (1950). *Stain Technol.*, **25**, 95.
—— (1953). *J. Path. Bact.*, **65**, 355.
Rose, G. (1953). Personal communication.
Slocumb, C. H. (1953). *Proc. Mayo Clin.*, **28**, 655.
Sokoloff, L., Wilens, S. L., and Bunim, J. J. (1951). *Amer. J. Path.*, **27**, 157.
Von Glahn, W. C., and Pappenheimer, A. M. (1926). *Ibid.*, **2**, 235.
Wegener, F. (1939). *Beitr. path. Anat.*, **102**, 36.
West, H. F., and Newns, G. R. (1953). *Lancet*, **2**, 1123.
Zeek, P. M. (1952). *Amer. J. clin. Path.*, **22**, 777.

Arthrite rhumatismale et polyartérite noueuse

RÉSUMÉ

On présente cinq observations, comprenant des résultats d'autopsie, illustrant l'association entre l'arthrite rhumatismale et la polyartérite noueuse.

Dans quatre cas l'artérite disséminée compliquait apparemment un processus rhumatismal établi et typique, la pathogénie de l'arthrite étant essentiellement indépendante des lésions artérielles. Dans un cas l'artérite était une trouvaille accidentelle, dans les autres elle constituait une cause contribuante majeure de la mort. Un seul de ces quatre cas avait reçu de l'ACTH ou de la cortisone.

Dans le cinquième cas un bref épisode arthritique survint au cours d'une maladie diagnostiquée cliniquement et histologiquement comme polyartérite noueuse; à l'autopsie on trouva dans les articulations des altérations rhumatismales typiques, l'artérite articulaire faisant défaut.

On suggère que, bien que la polyartérite noueuse soit une complication rare de l'arthrite rhumatismale, l'association de ces deux affections est plus qu'une coïncidence. Ce qu'on en sait suggère que la distribution, la fréquence et la morphologie des lésions artérielles dans l'arthrite rhumatismale sont variables, allant d'une artérite benigne indéterminée à une polyartérite noueuse classique.

Artritis reumatoide y poliarteritis nodosa

SUMARIO

Se presentan los hallazgos clínicos y de autopsia en cinco casos que ilustran la asociación de la artritis reumatoide con la poliarteritis nodosa.

En cuatro de ellos la arteritis diseminada aparentemente complicaba un proceso reumático establecido y típico, la patogénesis de la artritis siendo esencialmente independiente de las lesiones arteriales. En un caso la arteritis fué un hallazgo casual, en los demás constituyó una causa contribuyente mayor de la murte. Un solo de los cuatro casos había recibido la ACTH o la cortisona.

En el quinto caso un breve episodio artrítico ocurrió en el curso de una enfermedad diagnosticada clínica e histológicamente como poliarteritis nodosa; en la autopsia encontráronse en las articulaciones alteraciones reumáticas típicas, la arteritis articular siendo ausente.

Se sugiere que, aunque la poliarteritis nodosa sea una complicación rara de la artritis reumatoide, la asociación de estas dos afecciones es más que coincidente. Los datos disponibles sugieren que la distribución, la frecuencia y la morfología de las lesiones arteriales en la artritis reumatoide son variables, yendo desde la arteritis benigna indeterminada hasta la poliarteritis nodosa clásica.

PRELIMINARY CLINICAL TRIALS WITH 9-ALPHA-FLUORO HYDROCORTISONE ACETATE IN RHEUMATOID ARTHRITIS*

BY

EDWARD W. BOLAND and NATHAN E. HEADLEY

Los Angeles, California

(RECEIVED FOR PUBLICATION SEPTEMBER 29, 1954)

That the properties of adrenal cortical hormones may be modified by relatively minor alterations in their structural formulae is well known. Addition or removal of various chemical radicals and groupings at one or another carbon position in the steroid nucleus may enhance or lessen one or more of the physiological activities of the parent compound. The imagination of chemists has been so stimulated by this fact that literally hundreds of synthetic steroid preparations have been made, and at a rate more rapid than they can be tested therapeutically or experimentally in animals.

Because hydrocortisone and cortisone have definite limitations as treatment agents for rheumatoid arthritis, investigators have continued to search for substitutes which might be applied with greater success. We have screened a number of esterified preparations of hydrocortisone and have made clinical comparisons of their anti-rheumatic activity. Recently our attention was attracted to a halogen derivative, 9-alpha-fluoro hydrocortisone acetate, which, though probably not destined as a practical agent for systemic therapy in rheumatoid arthritis, is of interest because it exhibits far greater anti-rheumatic potency, milligram for milligram, than any steroid we have tested heretofore.

Clinical interest in the halogenated derivatives of hydrocortisone was stimulated by results of animal studies which indicated that these compounds possess unusually high glycogenic activity as measured by rat liver glycogen assays for 11-oxygenated corticoids. Fried and Sabo (1953, 1954), Borman and Singer (1954), and Borman, Singer, and Numerof (1954) determined that the 9-alpha-halo derivatives (chloro, fluoro, iodo, and bromo) manifest both glucocorticoid and mineralocorticoid properties, and each in differing degrees. With the fluoro compound, glycogen deposition activity was twice as great while its sodium-retaining effect was only one-fifth of that of the chloro derivative. Compared with cortisone acetate, 9-alpha-fluoro hydrocortisone acetate was much more potent in glycogenic activity (about 10 times), in producing thymus involution (four times), and in sodium retention.

Data concerning clinical trials with 9-alpha-fluoro hydrocortisone acetate are meagre. Goldfien and others (1954) found that the substance, administered orally as sole treatment and in extremely low dosage, was highly efficient in maintaining patients with Addison's disease; dosages as small as 0·25 to 1 mg. a day were sufficient to hold patients in a near optimal state. Metabolic studies conducted by these workers in Addisonian or bilaterally adrenalectomized patients demonstrated that the preparation caused marked retention of sodium and diuresis of potassium, and a striking and prolonged eosinopenic response. Comparative studies in a patient with Addison's disease disclosed that the compound's effect on electrolyte excretion was at least as powerful as that of aldosterone (electrocortin) and was considerably more prolonged. In female patients with adrenogenital syndrome 9-alpha-fluoro hydrocortisone acetate in total daily doses as low as 5 mg. caused marked reduction in urinary 17-ketosteroid excretion.

The immediate results of pilot trials with 9-alpha-fluoro hydrocortisone acetate in rheumatoid arthritis have recently been described (Boland, 1954; Bayles, 1954; Bunim, 1954). Incomplete and extremely brief observations made in a total of six patients suggested that the compound exerted a suppressive influence on the disease when taken orally in very small

* Based on material presented in a discussion at the annual meeting of the American Rheumatism Association, June, 1954. See p. 348.

daily amounts, but data were not sufficient to appraise adverse reactions or therapeutic practicability.

Present Investigation

The clinical response to orally administered 9-alpha-fluoro hydrocortisone acetate* was determined in thirteen patients with active peripheral rheumatoid arthritis. The drug was given as initial investigative treatment to seven patients who had received no therapy, other than conservative measures, for at least 3 months beforehand; in three of these medication was later transferred to hydrocortisone (free alcohol) in order to make dosage comparisons. Six patients, who had been maintained on established daily amounts of hydrocortisone (free alcohol) with satisfactory and stable clinical improvement, were transferred directly to the fluoro compound, and differences in dosage requirements for approximately equivalent degrees of rheumatic control were estimated.

* Supplies of 9-alpha-fluoro hydrocortisone acetate were made available to us by The Squibb Institute for Medical Research, New Brunswick, New Jersey, U.S.A. Hydrocortisone (free alcohol) was supplied by Merck and Co., Rahway, New Jersey, U.S.A.

9-alpha-fluoro hydrocortisone acetate was administered in divided doses four times a day, after meals and at bedtime. Changes in dosage were made by increases and decreases of 0·5 or 1·0 mg. each. No complemental medication was prescribed, but the patients were kept on sodium-poor (not quantitatively measured) diets. Three patients were observed under hospital conditions at the beginning and the others were followed as ambulatory outpatients throughout the period of study. The decision to employ small total daily dosages was based on reported animal and clinical data which indicated that the derivative possessed extraordinary metabolic potency.

Results in Patients receiving 9-Alpha-Fluoro Hydrocortisone Acetate as Initial Suppressive Therapy

With total initial suppressive dosages ranging from 4 to 8 mg. a day, subjective and objective improvement in the articular manifestations resulted in five of the seven patients (Table I). Improvement was slight or questionable in one patient (Case 6), and another (Case 7) experienced an acute articular

CLINICAL RESPONSE OF PATIENTS WITH RHEUMATOID ARTHRITIS TO INITIAL SU… DOSES

Case No.	Age (yrs)	Sex	Duration of Disease (yrs)	Activity of Disease	Initial Dosage (mg./day)	Onset of Improvement (hrs after first divided dose)	Degree & Rapidity Initial Clinical Improvement	Erythrocyte Sedimentation Rate (Westergren) (mm. per hr.) Before administration
1	55	F	4	Severe	4 × 2; 6 × 2; 8 × 4; 7 as maintenance dose	17 (after total of 3 mg.)	Marked 6 da…	96
2	48	F	7	Moderately severe	6 × 7; 5 × 3; 4 as maintenance dose	6 (after total of 2 mg.)	Marked 13 da…	58
3	59	F	8	Moderate	6 × 5; 5 × 3; 4 × 5; 3 × 8; transfer to hydrocortisone	7 (after total of 3 mg.)	Very m… in 7…	49
4	55	F	5	Moderately severe	4 × 21; transfer to hydrocortisone	30	Marked 14 d…	44
5	65	M	1	Moderate	4 × 14; transfer to hydrocortisone	24	Marked 14 d…	47
6	58	F	½	Moderately severe	4 × 4; 6 × 4; 7 × 5; transfer to hydrocortisone	? (Improvement too little and gradual to estimate)	Slight 13 d…	65
7	53	M	4	Moderate	4 × 7; discontinuance	Worse after 72 hrs	Worse	33

exacerbation involving multiple joints 72 hrs after initiation of the drug. In the five patients who demonstrated definite benefits, the onset and subsequent rate of improvement were rapid. The erythrocyte sedimentation rate was reduced promptly and strikingly in four of the seven patients. The degree and speed of overall improvement in five of the seven patients compared favourably with that which would have been expected from hydrocortisone or cortisone administered in much larger initial suppressive doses. These observations indicated to us that 9-alpha-fluoro hydrocortisone acetate exerts potent anti-rheumatic action when administered in relatively very small total daily doses.

Comparisons of Maintenance Dosage Requirements for 9-Alpha-Fluoro Hydrocortisone Acetate and Hydrocortisone (Free Alcohol)

Attempts were made in nine patients to estimate differences in dosage requirements for the maintenance of similar degrees of rheumatic control (Table II, overleaf). One patient (Case 16), who had been held under satisfactory clinical control with 50 mg. hydrocortisone (free alcohol) per day, was transferred to 9-alpha-fluoro hydrocortisone acetate in doses of 5 mg. a day, and 4 days later experienced a severe articular relapse. Dosage comparisons were not permitted in this case because marked fluid retention and moderate hypertension also developed and these prohibited trials with larger doses of the fluoro compound. From comparisons made in the remaining eight patients, the calculated dosage ratios of hydrocortisone (free alcohol) to 9-alpha-fluoro hydrocortisone acetate ranged from 8·3 : 1 to 12·5 : 1. Thus it appeared from clinical appraisals alone that the milligram anti-rheumatic potency of 9-alpha-fluoro hydrocortisone acetate was roughly ten times greater than that of hydrocortisone (free alcohol).

Adverse Reactions

During the short periods of observation embraced by this study, and with the dosage range explored, two adverse reactions to 9-alpha-fluoro hydrocortisone acetate were prominent: fluid retention and blood pressure elevation.

Retention of fluid, as manifested by oedema and/or sudden gains in weight, was observed in twelve of

DOSES OF 9-ALPHA-FLUORO HYDROCORTISONE ACETATE ADMINISTERED ORALLY

Degree Rapidity Initial Clinical Improvement	Erythrocyte Sedimentation Rate (Westergren) (mm./hr)		Duration of Administration (days)	Fluid Retention		Other Effects; Miscellaneous Comments
	Before Administration	Rapidity of Change with Administration		Objective Oedema	Sudden Weight Gain	
Marked 6 days	96	29 after 8 days	81	Moderate to slight (variable)	None	Slight elevation of blood pressure
Marked 13 days	58	25 after 10 days	77	Slight	10 lb. during first 10 days on doses of 6 and 5 mg./day; no further gain on 4 mg./day	Moderate elevation of blood pressure; moderate insomnia on 6 mg./day, slight on 4 mg./day; slight facial mooning after 4 weeks administration; irregular nausea after 8 weeks
Very marked in 7 days	49	16 after 10 days	21	Marked on doses of 6 and 5 mg./day; moderate on doses of 3 mg./day	13 lb. during first 13 days on doses of 6, 5, and 4 mg./day	Moderate elevation of blood pressure. After transfer to hydrocortisone (free alcohol) evidences of fluid retention disappeared within 5 days and blood pressure returned to pretreatment level in 14 days
Marked 14 days	44	16 after 10 days	21	Moderate	4½ lb. during first 5 days; then no further gain	Slight elevation of blood pressure. After transfer to hydrocortisone (free alcohol) evidences of fluid retention disappeared and blood pressure returned to normal in 5 days
Marked 14 days	47	34 after 14 days	14	Moderate	10 lb. in 14 days	Evidences of fluid retention disappeared 4 days after transfer to hydrocortisone (free alcohol)
Slight 13 days	65	48 after 13 days	13	None	None	Improvement only slight, even questionable; definite improvement later, after transfer to hydrocortisone (free alcohol)
Worse	33	23 after 7 days	7	Moderate	5 lb. in 7 days	Acute articular flare-up after 72 hrs of administration; subsidence followed withdrawal. History of similar exacerbation after 1 week of cortisone therapy 2 years previously. Refused trial on hydrocortisone

MAINTENANCE DOSAGE REQUIREMENTS FOR 9-ALPHA-FLUORO HY... ONE ACE...

Case No.	Activity of Disease	Improvement maintained with Both Compounds	Daily Dosages required for Equivalent Rheumatic Control (mg.)		Calculated Dosage Ratios (Hydrocortisone (free alcohol) : 9-alpha-fluoro Hydrocortisone Acetate)	Fluid Retention on Maintenance Doses		Blood Pr... Mai...
			Hydrocortisone (free alcohol)	9-alpha-fluoro Hydrocortisone Acetate		Hydro-cortisone (free alcohol)	9-alpha-fluoro Hydro-cortisone Acet...	cortisone alcohol)
8	Moderate	Very marked	25	3	8·3 to 1	None	Moderate	light
9	Moderately severe	Marked	40	4	10·0 to 1	None	Moderate	None
10	Moderate	Marked	40	4·5	8·9 to 1	None	Moderate	None
11	Moderately severe	Very marked	30	3	10·0 to 1	None	Slight	None
12	Moderately severe	Marked	50	5	10·0 to 1	None	Moderate	None
13	Moderately severe	Marked	35	4	8·8 to 1	None	Marked	None
14	Moderately severe	Marked	50	4	12·5 to 1	None	Marked	None
15	Moderate	Marked	35	3·5	10·0 to 1	None	Slight	None
16	Moderately severe	Marked on hydro-cortisone. Relapse on fluorohydro-cortisone	50	? (greater than 5)	—	Slight	Marked	light

the thirteen patients, marked in four, moderate in five, and slight in three. Signs of fluid retention usually began after 2 to 6 days of administration, and, when pronounced, it was accompanied by weight increases as great as 1 to 2 lb. per day. In order that this effect could be observed uninfluenced by countermeasures, diuretics were not employed. In each instance where the patient was transferred to hydrocortisone (free alcohol) in larger but equally efficient amounts, signs of fluid retention disappeared quite promptly, ordinarily within 2 to 5 days. These observations suggested that the substitution of a fluorine atom at the ninth carbon position of hydrocortisone enhanced not only the anti-inflammatory activity of the steroid but also its salt and water retaining property to an even greater degree.

Blood pressure elevations were recorded in six of the thirteen patients; these were regarded as slight in three and moderate in three. In each instance where transfer to hydrocortisone (free alcohol) was made the blood pressure returned to its former level within 4 to 14 days.

The treatment periods with 9-alpha-fluoro hydrocortisone acetate were too brief to permit assessment of other possible endocrine side-effects. One patient (Case 2), who received the preparation in maintenance dosages of 4 mg. a day for a total of 77 days, exhibited slight, questionable, facial mooning after 4 weeks of administration.

Two unusual reactions were observed. One patient (Case 12) suddenly experienced dryness of the mouth, a "toxic" feeling, and low-grade fever after the fluoro compound had been taken for 14 days; the symptoms disappeared 2 days after resumption of hydrocortisone (free alcohol) therapy. Another patient (Case 13) developed abdominal bloating, moderate facial oedema, and Grade II albuminuria with cylindruria but without azotaemia after 13 days of medication; the manifestations were corrected within 5 days of transfer to hydrocortisone (free alcohol). Two other patients complained of intermittent nausea.

Comment

The number of cases studied were too few and the periods of observation too short to allow more than limited and provisional deductions. However, it was obvious to us that the powerful salt and water retaining properties of 9-alpha-fluoro hydrocortisone, and perhaps other metabolic effects which may ensue with prolonged administration, would probably prohibit its employment as systemic medication for rheumatoid arthritis. Dosages of the order of 3 to 8 milligrams a day seemed to be necessary to provide adequate suppression of rheumatic manifestations when the disease was of moderate or greater activity. Even with these relatively small total daily amounts, most of the patients developed evidences of fluid

ONE ACETATE AND HYDROCORTISONE (FREE ALCOHOL) COMPARED

Blood Pressure Elevations on Maintenance Doses		Miscellaneous Comments
cortisone alcohol)	9-alpha-fluoro Hydrocortisone Acetate	
Slight	Moderate	
None	None	
None	None	
None	Slight	Nausea with 9-alpha-fluoro hydrocortisone acetate; none with hydrocortisone (free alcohol)
None	Moderate	After 2 weeks 9-alpha-fluoro hydrocortisone acetate developed sudden dryness of mouth, "toxic feeling", and low-grade fever. Symptoms disappeared 2 days after transfer to hydrocortisone (free alcohol)
None	None	After 13 days 9-alpha-fluoro hydrocortisone acetate developed abdominal bloating, moderate facial oedema, gr. 2 albuminuria without azotaemia. Symptoms disappeared 4 days after transfer to hydrocortisone (free alcohol)
None	None	
None	Slight	
Slight	Moderate	Pronounced articular relapse 4 days after transfer to 9-alpha-fluoro hydrocortisone acetate. Fluid retention and blood pressure elevation disallowed trial of larger doses

retention which in some were pronounced and intolerable. The fact that this complication disappeared promptly when treatment was changed to hydrocortisone (free alcohol) in larger but equally efficient doses signified that the substitution of a fluorine atom at the ninth carbon position of hydrocortisone enhances its salt-retaining effect more than its anti-phlogistic action.

These observations are of interest chiefly because they demonstrate that it is possible to enhance the anti-inflammatory activity of hydrocortisone, as well as to modify other of its properties, by altering its chemical structure. This implies that it is not beyond the realm of hope that, through other substitutions or changes in chemical configuration, a derivative of hydrocortisone may be prepared which, in effective anti-rheumatic doses, may be devoid of significant complications.

Summary

A halogenated derivative of hydrocortisone—9-alpha-fluoro hydrocortisone acetate—was administered as investigative therapy to thirteen patients with active rheumatoid arthritis. Seven patients received the preparation as initial medication; three were transferred later to hydrocortisone (free alcohol) for comparison of dosage requirements. Six patients who were being maintained on established daily amounts of hydrocortisone (free alcohol) were transferred directly to the fluoro compound and the doses needed for similar degrees of rheumatic control were compared.

The following conclusions were drawn:

(1) Weight for weight, the anti-rheumatic potency of 9-alpha-fluoro hydrocortisone acetate was found to be much greater than that of the parent compound, hydrocortisone. This was indicated by the following:

(*a*) Initial suppressive doses of the fluoro derivative ranging from 3 to 8 mg. a day were sufficient, in five of seven patients, to promote rapid improvement in the rheumatic manifestations;

(*b*) Comparisons of maintenance dosage requirements for approximately equivalent degrees of clinical control revealed that, in eight of nine patients, the anti-rheumatic power of 9-alpha-fluoro hydrocortisone acetate, milligram for milligram, was roughly ten times that of hydrocortisone (free alcohol).

(2) With the small total daily amounts of the fluoro compound employed, fluid retention developed in twelve of the thirteen patients, and became pronounced in some. This suggested that the substitution of a fluorine atom at the ninth carbon position increased the electrolytic activity of hydrocortisone more than it enhanced its anti-phlogistic property. The excessive salt and water retaining

effect of the fluoro derivative would seem to preclude its use as practical systemic therapy in rheumatoid arthritis.

(3) These observations demonstrate that the anti-inflammatory potency of hydrocortisone may be enhanced, and other of its properties modified, by altering its formula. This raises a hope that, through changes in structure or other chemical substitutions, a more successful therapeutic agent for rheumatoid arthritis may be produced in the future.

REFERENCES

Bayles, T. B. (1954). *Annals of the Rheumatic Diseases*, 13, 000.
Boland, E. W. (1954). *Ibid.*, 13, 000.
Borman, A., and Singer, F. M. (1954). *Fed. Proc.*, 13, 185.
——, ——, and Numerof, P. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, 86, 570.
Bunim, J. J. (1954). *Annals of the Rheumatic Diseases*, 13, 000.
Fried, J., and Sabo, E. F. (1953). *J. Amer. chem. Soc.*, 75, 2273.
——, —— (1954). *Ibid.*, 76, 1455.
Goldfien, A., Laidlaw, J. C., and Thorn, G. W. (1954). *New Engl. J. Med.* In the press.

Essais cliniques préalables de l'acétate de 9-alpha-fluoro hydrocortisone dans l'arthrite rhumatismale

RÉSUMÉ

Un dérivé halogène d'hydrocortisone—acétate de 9-alpha-fluoro hydrocortisone—fut administré, à titre d'enquête thérapeutique, à treize malades atteints d'arthrite rhumatismale active. A sept malades on donna cette préparation comme médication initiale; on soumit ensuite trois d'entre eux à l'hydrocortisone (alcool libre), pour comparer les doses requises. Six malades recevant jusqu'alors des doses quotidiennes fixes d'hydrocortisone (alcool libre) furent assignés au dérivé fluoré. On compara les doses nécessaires pour obtenir la même mesure d'amélioration de leur rhumatisme. On a tiré des conclusions suivantes:

(1) A poids égal, le pouvoir antirhumatismal de l'acétate de 9-alpha-fluoro hydrocortisone fut très supérieur à celui du composé parent, hydrocortisone, pour des raisons suivantes:

(*a*) Pour le traitement d'attaque, des doses quotidiennes de 3 à 8 mg. de dérive fluoré furent suffisantes chez cinq malades sur sept pour améliorer rapidement leurs manifestations rhumatismales.

(*b*) En comparant les quantités requises pour maintenir une mesure similaire d'amélioration clinique, on trouva que chez huit malades sur neuf le pouvoir antirhumatismal de l'acétate de 9-alpha-fluoro hydrocortisone, milligramme pour milligramme, fut à peu prés dix fois supérieur à celui de l'hydrocortisone (alcool libre).

(2) Malgré les doses quotidiennes totales faibles de composé fluoré, on observa chez douze sur treize malades une rétention aqueuse qui chez certains d'eux devint prononcée. Cela suggère que la substitution d'un atome de fluor à la neuvième position du carbone augmente l'action électrolytique plus que l'antiphlogistique de l'hydrocortisone. Cette propriété de retenir un excès de sel et d'eau semble anéantir l'application pratique du dérivé fluoré dans l'arthrite rhumatismale.

(3) Ces observations montrent qu'en changeant la formule on peut augmenter le pouvoir anti-inflammatoire de la cortisone et modifier ses autres propriétés. Cela permet d'espérer qu'on créera un jour un agent thérapeutique plus efficace contre l'arthrite rhumatismale par un changement de la structure ou par une autre substitution chimique.

Ensayos clínicos preliminares del acetato de 9-alfa-fluoro hidrocortisona en la artritis reumatoide

SUMARIO

Un derivado halógeno de hidrocortisona—acetato de 9-alfa-fluoro hidrocortisona—fué administrado, como terapia investigadora, a trece enfermos con artritis reumatoide activa. Siete enfermos recibieron esta preparación como medicación inicial; tres de ellos fueron luego trasladados a hidrocortisona (alcohol libre) para comparar las dosis requeridas. Seis enfermos tratados anteriormente con dosis diarias fijas de hidrocortisona (alcohol libre) fueron sometidos directamente al tratamiento con el compuesto de fluor, comparándose las dosis requeridas para el grado similar de control del reumatismo.

Se concluyó lo siguiente:

(1) A peso igual, el poder antirreumático del acetato de 9-alfa-fluoro hidrocortisona fué mucho mayor que él del compuesto pariente, la hidrocortisona, lo que fué indicado por lo siguiente:

(*a*) Dosis iniciales supresoras de 3 a 8 mg. por dia del derivado de fluor fueron suficientes, en cinco de los siete enfermos, para motivar una mejoria rápida de las manifestaciones reumaticas.

(*b*) Al comparar las dosis requeridas para mantener un control clínico de grado aproximadamente equivalente, se halló que la potencia antirreumática del acetato de 9-alfa-fluoro hidrocortisona, miligramo por miligramo, fué cerca de diez veces mayor que la de la hidrocortisona (alcohol libre).

(2) A pesar de la pequeñez de las dosis diarias totales del compuesto de fluor, sobre trece enfermos doce acusaron una retención hídrica que en algunos llegó a ser pronunciada. Esto sugiere que la sustitución de un átomo de fluor en la novena posición del carbón aumenta mas la acción electrolítica que la antiflogística de la hidrocortisona. Esta acción retentiva de sal y de aqua en exceso impediría la aplicación práctica del compuesto de fluor en la artritis reumática.

(3) Estas observaciones muestran que cambiando la formula se puede aumentar el poder anti-inflamatorio y modificar otras propiedades de la cortisona. Esto permite esperar que se llegará a producir por un cambio de la estructura o por otra sustitución química un mejor agente terapéutico contra la artritis reumatoide.

LOCAL ANTI-RHEUMATIC EFFECTIVENESS OF HIGHER ESTERS AND ANALOGUES OF HYDROCORTISONE*†

BY

JOSEPH L. HOLLANDER, ERNEST M. BROWN, JR., RALPH A. JESSAR, LOUIS UDELL, NATHAN SMUKLER, and MORRIS A. BOWIE

From the Arthritis Section, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pa

(RECEIVED FOR PUBLICATION OCTOBER 4, 1954)

During the past 3½ years we have given more than 17,000 intrasynovial injections of hydrocortisone (Compound F) into the joints, bursae, or tendon sheaths of nearly 1,300 patients for various forms of rheumatic disease (Hollander and others, 1951a, 1954; Brown and others, 1953; Hollander, 1953a,b). Numerous confirmatory and supplementary reports in the world medical literature have shown that this method has now been widely accepted as an adjunct in the local management of arthritis and related conditions (See Bibliography).

While we have found that intra-articular hydrocortisone acetate (F a) produces a temporary alleviating effect in over 80 per cent. of all joints injected, the transitory nature of this effect limits its practical value as therapy in about one-third of our cases. Obviously, joint injections cannot be repeated every few days, even on hospitalized patients. Since the method has proved of value mainly in helping to preserve normal joint function in ambulatory patients who would otherwise be disabled by some local rheumatic inflammation, a search has been conducted to find an agent capable of prolonging the local palliative effect.

Investigations into the disappearance of hydrocortisone from the synovial fluid, which revealed the absorption of the injected hormone by the cells of the synovial fluid and particularly by the lining membrane of the synovium, were reported by us a year ago (Hollander, 1953c, Zacco and others, 1954). The most significant finding was that the hydrocortisone acetate was apparently absorbed and retained by the lining of the synovium without splitting the ester, whereas unabsorbed hormone remaining in the joint fluid was rapidly hydrolysed and broken down.

We therefore assumed that higher, and less soluble, esters of hydrocortisone would likewise be absorbed unchanged by the synovial membrane, and might have a longer anti-inflammatory effect. Sterile microcrystalline suspensions of such higher esters and some analogues of hydrocortisone were formulated for us in the laboratories of Merck and Co.

Method

Our method of comparing the relative effectiveness of the various hydrocortisone esters has been simple. Patients with rheumatoid arthritis, or osteo-arthritis, who had previously been receiving periodic F a injections into an arthritic knee were studied exclusively. No change was made in general supportive or systemic therapy for the arthritis during the period of comparison. Since all the preparations appeared identical in the syringe, it was easy to keep the knowledge of any substitution from the patient. All comparisons were based on identical doses of hormone. Follow-up examinations were made on each patient to determine the extent and duration of the ameliorative effect of the injection on the symptoms and signs of the inflamed and painful joint. The effects were recorded and compared with similar observations made after F a injections. If comparative effects were equivocal, subsequent injections alternating the two preparations were carried out. In a few cases where both knees were about equally inflamed, simultaneous comparisons were possible. While most cases chosen were those having a transitory effect from hydrocortisone acetate, some others having had a relatively long effect were also studied.

The preparations thoroughly studied included two analogues of hydrocortisone: 9-alpha-chloro hydrocortisone (9-a-c F), and allo-dihydro hydrocortisone (A-d F). In addition to the standard hydrocortisone acetate (F a), we also studied hydrocortisone tertiary butyl acetate (F t-B a), hydrocortisone caprylate (F Cap.), and hydrocortisone benzoate (F Benz.). Others are still being assayed.

Results

The largest series was one of 171 cases of rheumatoid arthritis or osteo-arthritis (about equal numbers

* Read before the Annual Meeting of the American Rheumatism Association, San Francisco, Cal., June 18, 1954. See p. 354 of this issue.

† Supported by grants from the Helon Augusta Parkhill Memorial Fund, and from Merck and Co., Inc.

of each) in which hydrocortisone tertiary butyl acetate was substituted for hydrocortisone acetate. Comparative results, summarized in Table I, varied tremendously both in degree and in the duration of the alleviating effect. Of the 171 cases, 111 (65 per cent.) demonstrated greater alleviation of symptoms and signs from F t-B a, 51 (30 per cent.) showed no appreciable difference, and in nine (5 per cent.) the action of the higher ester was inferior to that of the standard F a.

TABLE I

COMPARATIVE EFFECTIVENESS OF INTRA-ARTICULAR HYDROCORTISONE TERTIARY BUTYL ACETATE AND HYDROCORTISONE ACETATE

Result		F t–Ba Superior	F t–Ba = F a	F a Superior	Total
Degree of Clinical Improvement	No. of Cases	111	51	9	171
	Percentage	65	30	5	100
Duration of Clinical Improvement	No. of Cases	101	59	11	171
	Percentage	59	35	6	100

Much more easily measured was the *duration* of relief after injections. By this we found that in 101 cases (59 per cent.) the duration of effectiveness was increased by at least 3 days, and was often multiplied from two to ten times by F t-B a as compared with F a. In 59 cases (35 per cent.) no significant difference in effect was noted, and in eleven cases (6 per cent.) F t-B a produced a shorter period of relief than F a.

By the simple method of adding together total days of symptomatic relief in all 171 cases after one injection each of hydrocortisone acetate (total 1,578) and then dividing by 171, we found the average duration of effectiveness after each was 9 days. Repeating this with the data from cases injected with hydrocortisone t-butyl acetate (total 2,745) we found the average duration of effectiveness from each injection to be 16 days.

There were four (2·3 per cent.) post-injection exacerbations of symptoms in the treated joint following F a in this series, and three (1·8 per cent.) following F t-B a injection. This difference is probably not significant.

Using the more easily measured, and apparently more critical, *duration of effectiveness* as a criterion for comparison, we assayed the relative effectiveness of other analogues and esters of hydrocortisone in seventeen patients with rheumatoid arthritis. Table II shows how variable the comparative duration of response can be after the injection of any of the preparations. The 9-alpha-chloro hydrocortisone (9-a-c F, col. 1) produced an average of 8 days' relief, as compared with 6 days from hydrocortisone acetate in the same joints (col. 3). Allo-dihydro hydrocortisone (A-d F, col. 2) produced no alleviation in eleven cases, a transient response in five, and alleviation of symptoms in one joint for 6 days. Therefore, the average period of effect was less than 1 day following this preparation. In these seventeen patients the hydrocortisone t-butyl acetate (col. 4) produced from 6 to 30 days alleviation (average 12). Hydrocortisone caprylate (F Cap., col. 5) averaged little better than F a (7 days), though in two instances the alleviation was longer than that obtained from any other injected preparation. The last column of Table II shows the results from the injection of hydrocortisone benzoate (F Benz.). While the duration of effect in nine cases averaged 8 days, further trial was abandoned because of the high incidence of rather severe post-injection reactions (indicated by *r*) in the injected joints, which meant that the preparation itself was an irritant.

TABLE II

DURATION OF EFFECT FROM 9-ALPHA-CHLORO HYDROCORTISONE, ALLO-DIHYDRO HYDROCORTISONE, HYDROCORTISONE ACETATE, HYDROCORTISONE T-BUTYL ACETATE, HYDROCORTISONE CAPRYLATE, AND HYDROCORTISONE BENZOATE INJECTED INTRA-ARTICULARLY INTO SEVENTEEN RHEUMATOID ARTHRITIC KNEES

Case	9-a-c F	A-d F	F a	F t-Ba	F Cap.	F Benz.
a	6	0	4	9	3	—
b	7	0	10	9	3	11(*r*)
c	6	0	6	6	6	—
d	7	0	2	6	1	—
e	11	0	14	14	14	3
f	8	0	7	14	16	—
g	10	0	8	13	—	10
h	4	2	2	4	4	—
i	9	0	7	12	8	14
j	9	0	10	30	13	—
k	7	6	2(*r*)	11	5(*r*)	1(*r*)
l	11	0	4	14	—	4(*r*)
m	6	0	5	7	18	—
n	2	2	2	7	2	—
o	9	1	5	14	0	14
p	7	1	8	8	8	7
q	8	1	9	12	0	7(*r*)
Average No. of Days	8	1	6	12	7	8
Duration Quotient*	1·3	0·16	1·0	2·0	1·16	1·3

* Average number of days of effect from F x divided by the average number of days of effect from F a.
(*r*) Initial exacerbation occurred after injection, then days of improvement followed as indicated.

As a ready means of comparing effectiveness of the various hydrocortisone preparations, the average number of days of beneficial effect from injection of each preparation is divided by average days of benefit following injection of the "standard" hydrocortisone acetate, to reach what we have termed a "duration quotient". This figure shows the superiority of hydrocortisone t-butyl acetate to the other preparations.

Discussion

While the mode of action of hydrocortisone at the tissue level is still unknown, it might at first appear from the results that our original premise is borne out. Whether the longer duration of benefit resulting from the intra-articular injection of hydrocortisone t-butyl acetate is merely due to its being a less soluble preparation, thus leading to slower tissue utilization, remains to be determined. If solubility alone were the factor determining length of action, then other higher esters of hydrocortisone, likewise much less soluble than the acetate, should have at least a comparable effect. But such was not the case.

Why hydrocortisone t-butyl acetate produces a longer period of palliation in a mere majority of cases, and shows no advantage over the acetate in others, cannot be adequately explained. It seems peculiar that in certain individuals the injection of hydrocortisone caprylate produced an amelioration of arthritis superior both in degree and duration to any of the other preparations studied. This superiority was repeatable consistently in these cases, yet in most others this preparation proved inferior to the rest. A few other such inconsistencies appeared on using other preparations. May it be that the synovial membranes of individuals differ in ability to absorb and utilize certain hydrocortisone preparations? Since the degree and duration of palliation obtained from hydrocortisone injection have no correlation with the intensity or length of existence of the synovial irritation, or even indeed with the type of arthritis present, the answer is certainly not yet forthcoming.

One fact, however, does emerge from these studies. In most arthritic individuals the intra-articular injection of certain analogues or higher esters of hydrocortisone can amplify both the degree and duration of the local hormone effect. The way is, therefore, open to finding other analogues or esters of hydrocortisone having a still more lasting palliative effect, which should render intra-articular hydrocortisone therapy of greater practical value as an adjuvant in the local management of a variety of rheumatic conditions.

Summary

(1) Hydrocortisone t-butyl acetate (F t-B a) injected intra-articularly into the arthritic knees of 171 patients has produced a greater and longer lasting palliation than identical doses of hydrocortisone acetate (F a) in about 60 per cent. of patients. In about 35 per cent. of cases no advantage was noted, and in about 5 per cent. the hydrocortisone acetate was more effective.

(2) By similar comparison, two analogues of hydrocortisone, *i.e.* 9-alpha-chloro hydrocortisone (9-a-c F), and allo-dihydro hydrocortisone (A-d F), and two other higher esters, *i.e.* hydrocortisone caprylate (F Cap.), and hydrocortisone benzoate (F Benz), were clinically assayed in seventeen cases of rheumatoid arthritis. While benefit was increased in a few cases by one or another of these preparations, none gave such consistent improvement as hydrocortisone t-butyl acetate. In fact, the hydrocortisone benzoate proved impracticable because of synovial irritation, and the effect of the allo-dihydro hydrocortisone was markedly inferior to that of the hydrocortisone acetate in most cases.

(3) While the reason for the greater effectiveness in the local palliation of arthritic symptoms of certain higher esters of hydrocortisone remains unknown, the way appears open towards the discovery of even more effective hydrocortisone preparations for intra-articular use in the rheumatic diseases.

Addendum

Since this report was originally prepared and presented, we have had the opportunity of assaying 9-alpha-fluoro hydrocortisone acetate (9-a-f F a) intra-articularly in 37 cases of rheumatoid arthritis or osteo-arthritis. A local anti-inflammatory effect was noted clinically from an intra-articular injection as small as 3 mg., but in most cases 5 mg. was used. Although the effective dose was decidedly smaller, the benefits in no case exceeded that of hydrocortisone acetate in degree of palliation or in duration of effect, and the duration quotient was less than 0·5. Whenever the dose was increased to 7·5 mg. into one knee, or 5 mg. into each knee, marked oedema of the leg or legs appeared and persisted for several days even though the patient was receiving no systemic cortisone.

Our findings thus confirm the marked increased anti-inflammatory potency of 9-alpha-fluoro hydrocortisone acetate noted by Boland and Headley (1954), and the increased salt retention noted by Liddle and others (1954). This latter effect would seem to nullify the advantage of the increased potency, at least for intra-articular use.

References

Brown, E. M., Jr., Frain, J. B., Udell, L., and Hollander, J. L. (1953). *Amer. J. med.*, **15**, 656.
Hollander, J. L. (1953a). *J. Bone Jt Surg.*, 35A, 983.
—— (1953b). *Ann. intern. Med.*, 39, 735.
—— (1953c). *Annals of the Rheumatic Diseases*, **12**, 347.
——, Brown, E. M., Jr., and Jessar, R. A. (1954). *Med. Clin. N. Amer.*, **38**, 349.
—— —— ——, and Brown, C. Y. (1951a). *J. clin. Invest.*, **30**, 650.
Zacco, M., Richardson, E. M., Crittenden, J. O., Hollander, J. L., and Dohan, F. C. (1954). *J. clin. Endocr.*, **14**, 711.

ADDITIONAL BIBLIOGRAPHY

Ballabio, C. B., Sala, G., and Bonomo, E. (1953). *Reumatismo*, **5**, 259.
Bauer, J. (1954). *Münch. med. Wschr.*, **96**, 309.
Bilka, P. J. (1952). *Minn. Med.*, **35**, 938.
Boland, E. W. (1952). *Calif. Med.*, **77**, 1.
——, and Headley, N. E. (1954). *Annals of the Rheumatic Diseases*, **13**, 291.
Böni, A. (1953). *Praxis*, **42**, 702.
Bornstein, J., Silver, M., Neustadt, D. H., Berkowitz, S., and Steinbrocker, O. (1954). *Geriatrics*, **9**, 205.
Breck, C. A., and Breck, R. W. (1952). *Meriden Hosp. Bull.*, **6**, 39.
Brown, L. (1953). *S. Afr. med. J.*, **27**, 226.
Butson, A. R. C. (1954). *Canad. med. Ass. J.*, **70**, 51.
Copeman, W. S. C., Savage, O., Dodds, C., Glyn, J. H., and Fearnley, M. E. (1954). *Brit. med. J.*, **1**, 1109.
Coste, F., Piguet, B., and Civatte, J. (1953). *Presse méd.*, **61**, 1157.
Coventry, M. B. (1954). *Proc. Mayo Clin.*, **29**, 58.
Cozen, L. (1953). *Postgrad. Med.*, **14**, 59.
Cyriax, J., and Troisier, O. (1953). *Brit. med. J.*, **2**, 966.
Davison, S. (1953). *N.Y. St. med. J.*, **53**, 975.
Dixon, A. St. J. (1954). *Lancet*, **2**, 281.
Duff, I. F., Robinson, W. D., and Smith, E. M. (1951). *J. Lab. clin. Med.*, **38**, 805.
Ensign, D. C., and Sigler, J. W. (1952). *J. Mich. med. Soc.*, **51**, 1189.
Françon, J. (1953). *Presse therm. clim.*, **90**, 170.
Freeland, D. E., and Gribble, M. de G. (1954). *Lancet*, **2**, 225.
Freiberg, J. A. (1954). *Postgrad. Med.*, **16**, 104.
Freund, H. A. (1952). *J. Mich. med. Soc.*, **51**, 1199.
Henderson, E. D., and Henderson, C. C. (1953). *Minn. Med.*, **36**, 142.
Henriksen, E., and Nyfos, L. (1953). *Ugeskr. Laeg.*, **115**, 1763.
Hollander, J. L. (1951). *Bull. rheum. Dis.*, No. 2, p. 3.
——, Brown, E. M., Jr., Jessar, R. A., and Brown, C. Y. (1951b). *J. Amer. med. Ass.*, **147**, 1629.
Howard, L. D., Jr., Bunnell, S., and Pratt, D. R. (1953). *J. Bone Jt Surg.*, **35A**, 526.
Hurlburt, F. W. B., and Robinson, C. E. G. (1954). *Canad. med. Ass. J.*, **70**, 645.
Jessar, R. A., Ganzell, M. A., and Ragan, C. (1953). *J. clin. Invest.*, **32**, 480.
Kashtan, H. A. (1952). *Harper Hosp. Bull.*, **10**, 143.
Kersley, G. D., and Desmarais, M. H. L. (1952). *Lancet*, **2**, 269.
Krewer, B. (1954). *Presse méd.*, **62**, 543.
Lancet (1954). Leader, **1**, 448.
Liddle, G. W., Pechet, M. M., and Bartter, F. C. (1954). *Science*, **120**, 496.
Losada, M., and Zanartu, J. (1953). *Rev. med. Chile*, **81**, 261.
Mahaffey, H. W. (1954). *J. Amer. med. Ass.*, **156**, 312.
Mettier, S. R. (1954). *Gen. Pract. Clin.*, **10**, 89.
Murley, A. H. G. (1954). *Lancet*, **2**, 223.
Norcross, B. M. (1954). *N.Y. St. J. med.*, **54**, 347.
Orbach, E. J. (1952). *J. int. Coll. Surg.*, **18**, 159.
Pap, L. de, and Teixeira, M. A. (1953). *Rev. Rhum.*, **20**, 285.
Price, A. E., Reveno, W. S., Lightbody, J. J., Heide, E. C. V., Kashtan, H. A., and Corrigan, K. E. (1952). *J. Mich. med. Soc.*, **51**, 1183.
Quin, C. E., and Binks, F. A. (1954). *Lancet*, **2**, 221.
Quigley, T. B. (1954). *New Engl. J. Med.*, **250**, 188.
Ramsey, R. H., and Key, J. A. (1953). *Missouri Med.*, **50**, 604.
Reynolds, F. C., and Ramsay, R. H. (1954). *Sth. med. J. (Bgham Ala.)*, **47**, 209.
Robecchi, A., and Capra, R. (1952). *Minerva med. (Torino)* (Parte sci), **43** (2), 1259.
——, —— (1953). *Ibid.*, **44** (1), 997.
Sacks, S. (1953). *S. Afr. med. J.*, **27**, 224.
Sèze, S. de, Robin, J., Chevallier, J., and Françon, J. (1952a). *Presse méd.*, **60**, 1465.
——, ——, ——, —— (1952b). *Rev. Rhum.*, **19**, 985.
——, ——, ——, —— (1952c). *Bull. Soc. méd. Hôp. Paris*, **68**, 1045.
——, ——, and Debeyre, N. (1953). *Rev. Rhum.*, **20**, 298.
——, ——, and Denis, A. (1953). *Ibid.*, **20**, 303.
Shaw, C. C. (1954). *Postgrad. Med.*, **15**, 308.
Stein, I., Stein, R. O., and Beller, M. L. (1953). *Amer. J. Surg.*, **86**, 123.
Steinbrocker, O. (1953). *Indust. Med. Surg.*, **22**, 314.
Stevenson, C. R., Zuckner, J., and Freyberg, R. H. (1952). *Annals of the Rheumatic Diseases*, **11**, 112.
Weismann-Netter, R., Levy, R., and Lorch, P. (1954). *Presse méd.*, **62**, 852.
Weiss, T. E., Duncan, T., and de la Cruz, B. (1954). *J. med. Ass. Georgia*, **43**, 629.
Wilson, H. Fairbanks, R., and Scialabba, D. (1954). *J. clin. endocr.*, **14**, 814.
Young, H. H., Ward, L. E., and Henderson, E. D. (1954). *J. Bone Jt Surg.*, **36A**, 602.
Ziff, M., Scull, E., and Bunim, J. J. (1952). *Fed. Proc.*, **11**, 405.
——, ——, Ford, D., McEwen, C., and Bunim, J. J. (1952). *Arch. intern. Med.*, **90**, 774.
Ziff, M., Wilson, H., Scialabba, D., Scull, E., and Glyn, J. (1953). *J. clin. Invest.*, **32**, 614.
Zweifel, B. W. (1954). *Schweiz. med. Wschr.*, **84**, 447.

Effet antirhumatismal local des esters en position haute et des analogues d'hydrocortisone

RÉSUMÉ

(1) Le t-butyl acétate d'hydrocortisone (F t-Ba) en injection intra-articulaire dans les genoux arthritiques de 171 malades a produit un effet palliatif plus grand et plus durable que des doses identiques d'acétate d'hydrocortisone (Fa) chez environ 60 pour cent des malades. Dans 35 pour cent environ des cas on n'a pas vu de différence et chez environ 5 pour cent des malades l'acétate d'hydrocortisone a été plus efficace.

(2) De façon similaire, deux analogues d'hydrocortisone—9-alpha-chloro hydrocortisone (9-a-c F) et allo-dihydro hydrocortisone (A-d F)—ainsi que deux autres esters en position haute—caprylate d'hydrocortisone (F Cap.) et benzoate d'hydrocortisone (F Benz.)—ont été titrés cliniquement dans 17 cas d'arthrite rhumatismale. Bien que certaines préparations se soient montrées avantageuses ci et là, aucune d'elles n'a produit d'améliorations aussi constantes que le t-butyl acétate d'hydrocortisone. Le benzoate d'hydrocortisone s'est avéré peu pratique car il provoquait de l'irritation synoviale et l'effet de l'allodihydro hydrocortisone a été dans la plupart des cas nettement inférieur à celui de l'acétate d'hydrocortisone.

(3) Bien qu'on ne connaisse pas de raison de cette grande efficacité de certains esters en position haute d'hydrocortisone dans l'atténuation locale des symptômes arthritiques, on croit entrevoir le chemin de la découverte des préparations d'hydrocortisone encore plus efficaces par voie intra-articulaire dans les maladies rhumatismales.

ADDENDUM

Depuis la préparation et la présentation de ce rapport nous avons eu l'occasion de titrer l'acétate de 9-alpha-fluoro hydrocortisone (9-a-f Fa) par voie intra-articulaire dans 37 cas d'arthrite rhumatismale et d'ostéo-arthrite.

Nos résultats confirment que l'acétate de 9-alpha-fluoro hydrocortisone est un antiphlogistique bien plus fort (noté par Boland et Headley, 1954) et qu'il augmente la rétention sodique (noté par Liddle et coll., 1954). Ce dernier effet semble annuler l'avantage dérivant de sa plus grande puissance, tout au moins pour son emploi intra-articulaire.

Efecto antirreumático local de los ésters en posición alta y de los análogos de hidrocortisona

SUMARIO

(1) El t-butil acetato de hidrocortisona (F t-Ba) por inyección intra-articular en las rodillas artríticas de 171 enfermos produjo un efecto paliativo mayor y más prolongado que dosis idénticas de acetato de hidrocortisona (Fa) en cerca de 60 por ciento de ellos. En cerca de 35 por ciento de los casos no se observó ventaja alguna y en cerca de 5 por ciento de los enfermos el acetato de hidrocortisona fué más eficaz.

(2) De igual modo, dos análogos de hidrocortisona—9-alfa-cloro hidrocortisona (9-a-c F) y alo-dihidro hidrocortisona (A-d F)—así como dos otros ésters en posición alta—caprilato de hidrocortisona (F Cap.) y benzoato de hidrocortisona (F Benz.)—fueron avaluados clínicamente en 17 casos de artritis reumatoide. Aunque a veces algunas de estas preparaciones mostráronse

ventajosas, ninguna produjo mejorías tan consecuentes como el t-butil acetato de hidrocortisona. El benzoato de hidrocortisona, por causar irritación sinovia, no fué práctico y la alo-dihidro hidrocortisona mostrose en la mayoría de los casos netamente inferior al acetato de hidrocortisona.

(3) Aunque no se conozca la razón de esta gran eficacia de ciertos ésters en posición alta de hidrocortisona en la atenuación local de los síntomas artríticos, el camino parece abierto hacia la descubierta de preparaciones de hidrocortisona aun más eficaces para el empleo intra-articular en las enfermedades reumáticas.

ADDENDUM

Desde la preparación y la presentacion de este informe tuvimos oportunidad de avaluar el acetato de 9-alfa-fluoro hidrocortisona (9-a-f Fa) por vía intra-articular en 37 casos de artritis reumatoide y de osteoartritis.

Nuestros resultados confirman el aumento apreciable de la potencia anti-inflamatoria del acetato de 9-alfa-fluoro hidrocortisona (notada por Boland y Headley, 1954), y el aumento de la retención sódica (notada por Liddle y col., 1954). El último efecto parece anular la ventaja de la mayor potencia, al menos respecto a su empleo intra-articular.

PERIPHERAL VASCULAR EFFECT OF CORTISONE IN RHEUMATOID ARTHRITIS, SCLERODERMA, AND OTHER RELATED CONDITIONS

BY

B. N. CATCHPOLE, R. P. JEPSON, and J. H. KELLGREN
From the University Department of Surgery and Rheumatism Research Centre, Manchester Royal Infirmary

(RECEIVED FOR PUBLICATION JULY 9, 1954)

Many systemic diseases including rheumatoid arthritis are frequently associated with a diminution or redistribution of peripheral blood flow. This may be due to an organic arterial narrowing or occlusion or, alternatively, to a high resting tone in the peripheral vessels which may still be capable under certain conditions of relaxing to a normal calibre. Thus the vasodilatation in the fingers which normally follows heating of the trunk and legs was shown by Vulliamy (1952) to be absent in ten out of eleven cases of pink disease. Clinical recovery was associated with a return of this vasodilator response. A similar vasomotor defect was demonstrated by Woodmansey (1951) in cases of rheumatoid arthritis. Beattie and Woodmansey (1953) later showed that peripheral vasodilator response to heating in such cases could frequently be increased by an intravenous infusion of ACTH. Hines (1950) reported similar findings in three patients with acrosclerosis treated by cortisone.

The study reported in this paper concerns patients suffering from rheumatoid arthritis and other chronic systemic diseases in whom the fingers appeared cold and cyanosed with Raynaud's phenomenon or acrocyanosis on exposure to cold. In some patients nutritional lesions such as pulp

TABLE
PARTICULARS OF 22 PATIENTS INVESTIGATED

Diagnosis	Case No.	Sex	Age (yrs)	Duration (yrs)	Differential Sheep cell Agglutination Test	Erythrocyte Sedimentation Rate (mm./hr)	Delay of Flush after Occlusion (sec.)	Response to Cortisone						
								General Clinical	Circulatory (galvanometer reading)*					
									Resting		Reactive Hyperaemia		Body Heating	
									(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)
I Rheumatoid Arthritis	1	F	29	3	Positive	35	< 4	++	6	18	38	63	70	85
	2	F	53	14	Positive	45	< 4	++	3	130				
	3	F	42	1½	Positive	90	< 4	++	2	65				
	4	M	55	8	Positive	80	< 4	++	7	116				
	5	F	46	3	Positive	20	< 4	+	−2	25	6	32	95	55
	6	F	57	2	Negative	70	< 4	+	0	5	16	15	15	15
	7	M	31	8	Negative	80	< 4	++	35	69	33	68	51	70
II Non-Articular Rheumatoid Disease	8	F	28	7	Positive	55	4	+	10	85	14	90	47	104
	9	F	41	3	Positive	15	4	+	0	22	21	34	47	60
	10	F	25	1	Negative	2	15	o	2	0	1	3	3	7
	11	F	48	2	Positive	20	—	o	10	7				
	12	F	34	3½	Positive	20	4	+	4	8	4	21	35	62
III Systemic Sclerosis	13	F	21	8	Positive	25	>30	o	0	0	0	3	0	6
	14	F	24	13	Positive	50	>30	o	0	0	0	0	0	0
	15	F	53	3	Negative	34	5	o	−1	−4	2	−4	23	32
IV Miscellaneous	16	F	38	22	Positive	30	5	o	−7	4	−6	18	24	28
	17	F	30	6	Positive	11	>10	o	0	0	0	0	0	0
	18	M	40	8	Positive	40	25	o	0	1	4	1	11	1
	19	M	36	2½	Negative	30	10	+	5	55	14	42	15	75
	20	F	51	2	Negative	20	< 4	+	2	30	15	42	79	104
	21	F	48	20	Negative	20	> 5	+	2	2	2	6	10	46
	22	F	37	6	Negative	3	> 8	+	0	25	0	33	31	48

* (*a*) before treatment (*b*) during treatment.

ulcers or soft tissue atrophy were also present. An attempt was made to assess the degree and duration of their peripheral vascular response to cortisone therapy in terms of changes in digital blood flow estimated by a heat flow disk calorimetric technique and to correlate this response with the underlying disease process, other vascular and non-vascular tests, and the general therapeutic response of the patient to cortisone.

Patients Studied

The particulars of 22 in-patients investigated are set out in the Table. It will be noted that they have been grouped into four main diagnostic categories, though for many of the patients in Group IV no really satisfactory diagnostic label could be found.

Group I.—Seven patients considered to be suffering from typical rheumatoid arthritis by reason of their clinical and radiological joint lesions, a persistently raised erythrocyte sedimentation rate and in five a positive differential sheep cell agglutination test (D.A.T.).

Group II.—Five patients considered to be suffering from non-articular rheumatoid disease, who gave a history of limb pains with morning stiffness but without significant clinical or radiological changes in the joints. They had, however, marked nodular thickening of the long flexor tendons in the hands and in four of the five cases the D.A.T. was positive. In at least two patients (Cases 9 and 11) there was also definite sclerosis of the extremities.

Group III.—Three patients with established systemic sclerosis: that is, slowly progressive sclerosis and atrophy of the extremities associated with multiple joint and visceral lesions.

Group IV.—A miscellaneous group of seven patients, three considered to be suffering from dermatomyositis and its sequelae (Cases 19, 20, and 21), one from classical scleroderma of the trunk and limbs (Case 22), and three from multiple occlusive lesions in the small vessels of unknown aetiology associated with sclerosis of the extremities (Cases 16, 17, and 18).

If the term scleroderma is employed in its widest sense, it could be applied to all the patients in Groups III and IV and to at least two of the patients in Group II.

Methods

Estimations of finger blood flow were made before cortisone therapy was initiated:

(1) with the patient resting,
(2) after the application of a supra-systolic pneumatic cuff for 5 min. to the upper arm,
(3) after body heating.

These recordings were repeated after the administration of cortisone for 72 hrs (50 mg. 6-hrly), and finally 5 to 7 days after cessation of the cortisone therapy. In a few patients, however, cortisone therapy was continued for several months.

Modifications of finger blood flow were assessed by means of a copper-tellurium disk (Hatfield, 1950; Catchpole and Jepson, 1954). The disk, which has a diameter varying from 0·5-1·0 cm. and a thickness of 2-3 mm., consists of tellurium alloy covered on both faces by copper gauze. Leads from the faces of the disk connect with a mirror galvanometer (450 ohm). When one surface of the disk is maintained at a constant temperature, the potential difference which arises between the two faces of the disk allows the heat flow across the disk to be calculated in calories per unit area per unit time. Alternatively the disk may be used as a thermocouple, and under the conditions used in these experiments a temperature difference between the faces of 2·5° C. was equivalent to approximately 100 galvanometer divisions.

The disk was attached to the skin over the pulp of a finger with thin cellulose tape covered by a fine rubber finger stall, and the digit was immersed in a continuously stirred water bath, the temperature of which was maintained at 30° C. Readings were made from the galvanometer at minute or half-minute intervals. Conditions for each experiment were standardized, the subject resting lightly clothed on a couch in a draughtless temperature-controlled (21° C. $\pm\frac{1}{2}$°) room for at least 45 min. before the readings were begun. After the establishment of basal heat flow recordings, a reactive hyperaemia was induced by the application of a pneumatic tourniquet to the upper arm (50 mm. Hg above systolic blood pressure) for 5 min. Peripheral vasodilatation was obtained by heating the trunk and limbs of the patient, excluding the arm to be measured, with an electric blanket for 45 min.

This disk technique provides a useful index of finger blood flow which is particularly suitable for comparative studies of vascular responsiveness. Although figures for heat flow per unit area and time can be calculated from the galvanometer readings, they do not provide a more accurate index of blood flow changes than the original readings, so that these have been used throughout. Fig. 1 (overleaf), showing the records obtained from Case 1, serves to illustrate the nature of the data collected.

The presence or absence of organic disease of the digital arteries was assessed by a reactive hyperaemia timing test (Pickering, 1933), in which the hand was immersed to the wrist in water at 40° C. for 5 min., during which time a supra-systolic cuff was applied to the upper arm. On removal of the cuff the time taken for the resulting hyperaemia flush to reach the tips of the digits was estimated. An interval of

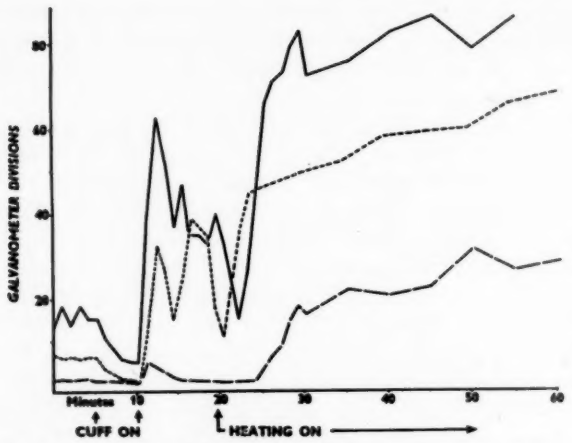


Fig. 1.—Recordings of finger skin heat flow in galvanometer divisions (Case 1).
.....: before cortisone.
————: during cortisone.
— — —: 7 days after cessation of cortisone.

4 sec. or less was taken as evidence of normal digital artery patency.

The general response of the patient to cortisone therapy in terms of symptomatic relief, improvement of functional capacity, and increased joint mobility was assessed and graded as nil (0), slight (+), or good (++). The erythrocyte sedimentation rate was estimated by the Westergren technique, and the differential sheep cell agglutination test by the method of Ball (1950).

Results

Group I (*Rheumatoid Arthritis: 7 patients*).—The seven patients in this group had normal digital artery patency as estimated by the reactive hyperaemia test. During the disk measurements at rest, the finger temperature was no higher than the water temperature in two, slightly higher in four, and definitely higher in one. In the five patients investigated by the reactive hyperaemia disk test, vasodilation following occlusion was present but of slight degree and duration, and these patients all showed a somewhat reduced peripheral vascular response to body heating. The administration of cortisone caused a marked increase of the resting blood flow and a greater quantitative response to temporary ischaemia. It was also noticed that the records reflected extraneous stimuli such as noise and conversation, indicating a generally more labile vasomotor state. These patients generally had a good clinical response to cortisone, as estimated by the sense of well-being, loss of pain, and freedom and strength of movement. After the withdrawal of the cortisone there was a deterioration in the general condition of the patients and a coincident reduction of the resting digital blood flow below the pre-cortisone level. In addition, the hyperaemia following temporary occlusion and body heating was markedly decreased (Fig. 1).

Group II (*Non-Articular Rheumatoid: 5 patients*).—There was some general and vascular response to cortisone therapy in three patients in whom the reactive hyperaemia timing test was at the upper limit of normal. Two patients (Cases 9 and 11), whose reactive hyperaemia time was delayed and who did not experience general improvement with the drug, also failed to manifest an improved peripheral blood flow. The "rebound" after cessation of therapy was similar to that in Group I.

Group III (*Systemic Sclerosis: 3 patients*).—These patients had evidence of gross organic arterial occlusion as demonstrated by the delayed reactive hyperaemia time, nutritional ulcers, and soft tissue atrophy of the extremities. During the heat flow disk test the finger temperature remained equal to that of the water bath (30° C.) and only in Case 15 did the 5-min. ischaemia or the body heating provoke a slight digital vasodilatation. The vascular reactions and the general and articular symptoms of these patients were not appreciably modified by cortisone therapy.

Group IV (*Miscellaneous: 7 patients*).—One patient in this group (Case 20) had a normal reactive hyperaemia time and showed a good circulatory and moderate general response to cortisone therapy. The other six had a delayed reactive hyperaemia time which varied from 5-25 sec. In general, the finger temperature on immersion was near that of the water bath. During cortisone therapy some change in blood flow was detected in those whose reactive hyperaemia was delayed less than 10 sec., but no change could be detected in the two (Cases 17 and 18) whose reactive hyperaemia was greater than 10 sec. A slight general symptomatic improvement was noted in four of the five patients showing vasodilatation during cortisone therapy.

The mean circulatory findings in the first three groups both before and during cortisone are illustrated in Fig. 2 (opposite). The findings in six normal individuals have been included for comparison.

Discussion

Recording of skin temperature by the heat flow disk technique does not allow absolute assessment of blood flow to be made. It does, however, provide a useful index of fluctuations or changes in cutaneous blood flow (Catchpole and Jepson, 1954). It is more satisfactory than the copper-constantum

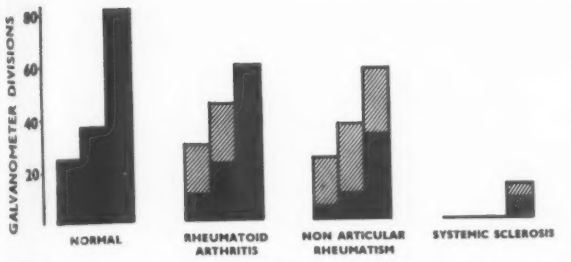


Fig. 2.—Mean values of finger skin heat flow in six normal subjects and in the patients listed in the Table.
Solid: before cortisone.
Hatched: during cortisone.
Left: resting level.
Centre: maximal heat flow following 5 minutes' occlusion.
Right: maximal heat flow during 45 minutes' body heating.

thermocouple technique, in that the test finger is kept in constant temperature water bath.

The patients reported in this study fall into two main groups: those who responded to cortisone therapy by a peripheral vasodilatation, and those who failed to respond.

In the former group evidence of increased peripheral blood flow was obtained from the higher resting temperature and the greater response to the vasodilator stimuli of ischaemia and trunk heating. This was accompanied in most instances by a diminution of articular pain and an improvement in strength and mobility.

The relationship between the circulatory response to cortisone and the state of the peripheral arterial tree as judged by the reactive hyperaemia timing test is shown in Fig. 3. It will be seen that a marked increase of digital blood flow during cortisone therapy only occurred when the reactive hyperaemia appeared in less than 5 sec. When the delay in this test was longer than 10 sec. cortisone had no effect whatsoever. Furthermore, those patients who experienced marked symptomatic relief from cortisone all showed some increase of digital blood flow, whereas those who experienced no symptomatic relief also showed no change in digital blood flow. Among the patients who obtained partial symptomatic relief from cortisone there were several who showed a large increase of finger blood flow and several in whom this was negligible or absent.

On the other hand, the presence of a positive differential sheep cell agglutination test did not appear to be associated with a good circulatory response to cortisone. Thus, of the fourteen patients in whom this test was positive, seven showed little or no increase of digital blood flow during cortisone therapy, but of the eight in whom the test was negative three showed a substantial increase.

The withdrawal of cortisone is known to cause a deterioration in the well-being of the patient, and

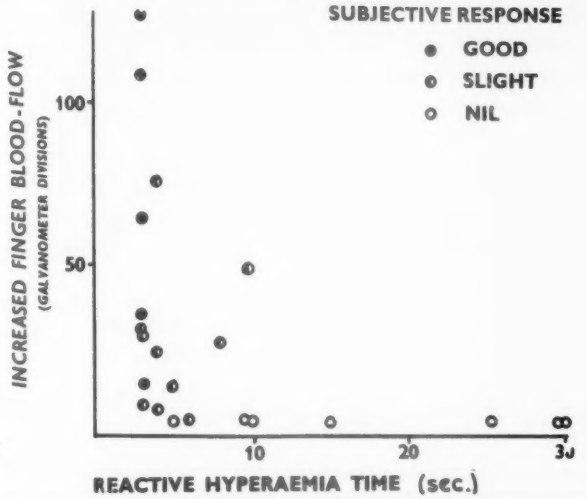


Fig. 3.—Relationship between reactive hyperaemia time, increase of resting heat flow during cortisone therapy, and subjective response to cortisone therapy in terms of relief of joint pain and stiffness. Each circle represents one patient.

is often accompanied by a return of previous joint pain and stiffness. A similar "rebound" was exhibited by the finger blood flow, which invariably diminished to below the pre-cortisone level.

The disturbance of the peripheral circulation in rheumatoid arthritis and some related conditions is peculiar, in that cold mauve extremities are associated with hot joints. After cortisone therapy or intra-articular hydrocortisone, the abnormally high joint temperature falls (Hollander and others, 1951). Plethysmographic studies of blood flow through the knee segment (Janus, 1952) have confirmed the increased knee blood flow in rheumatoid disease and have demonstrated that during cortisone or ACTH therapy this high knee blood flow falls towards normal levels at a time when finger blood flow is increasing; thus we are dealing with an abnormal distribution of blood flow in the limbs of these patients rather than a total increase or decrease. The mechanism by which this redistribution is brought about is unknown, but in patients with rheumatoid arthritis uncomplicated by occlusive arterial disease sympathectomy produces warm, dry extremities, although it does not relieve the arthritis. This suggests that the redistribution of the peripheral circulation in these patients is probably not a causal but a secondary phenomenon. The mechanism by which cortisone influences the peripheral circulation in these patients is equally unknown, but in one patient (Case 17), in whom a cervico-thoracic sympathetic ganglionectomy was performed, a course of cortisone given 3 months after the operation failed to provoke the moderate peripheral vasodilatation which was recorded before the operation.

This suggests that the peripheral vascular action of cortisone may, like nor-adrenaline (Barcroft and others, 1954), depend on the integrity of the sympathetic nervous system as well as on the patency of the peripheral vessels.

A disappointing finding was the complete absence of response to the short course of cortisone in the three patients with systemic sclerosis, the poor clinical response in most of the patients considered to have non-articular rheumatoid disease, and the complete absence of any improvement in peripheral circulation in two of these latter patients. In the miscellaneous group only those patients considered to be suffering from subacute dermatomyositis obtained some slight symptomatic relief from cortisone, and these also showed some improvement in their peripheral circulation. It was thought that more prolonged cortisone therapy might be more effective, and four patients (Cases 13, 14, 16, and 19) were given oral cortisone in a dosage of 100 mg. per day for periods of 1 to 3 months, but in none of these was there any further change. One of these patients (Case 16) developed fatal right heart failure. Autopsy material from this patient and biopsy material from Case 14 showed that the lumen of many smaller arteries was greatly reduced by a concentric fibro-mucoid intimal thickening, which would be in keeping with the circulatory findings and the absence of response to cortisone.

Although many of the patients investigated had clinical features suggestive of rheumatoid disease and had a positive sheep cell agglutination test, only those who had typical rheumatoid arthritis responded significantly to cortisone therapy. Whatever the pathological process may be in the other patients with limb pains, joint stiffness, reduced peripheral circulation, and a tendency to sclerosis and atrophy of the extremities, it does not appear to be greatly influenced by the short-term administration of cortisone. Long-term cortisone therapy might, however, be worthy of trial in those patients in whom the reactive hyperaemia timing test shows a delay of less than 10 seconds.

Summary

(1) The peripheral vascular response to short courses of cortisone has been studied by a heat flow technique in 22 patients suffering from rheumatoid disease, systemic sclerosis, and other related syndromes in which digital blood flow is reduced.

(2) During cortisone therapy there was a marked increase of digital blood flow in patients who experienced relief of joint pain and stiffness and in whom the reactive hyperaemia time was less than 5 seconds.

(3) The differential sheep cell agglutination test was positive in fourteen of the 22 patients investigated, but the presence of a positive test was not specially associated with a good symptomatic or vascular response to cortisone.

(4) After the withdrawal of cortisone the digital blood flow usually fell to below pre-treatment levels.

The cortisone used in these studies was provided by the Medical Research Council.

REFERENCES

Ball, J. (1950). *Lancet*, **2**, 520.
Barcroft, H., Gaskell, P., Shepherd, J. T., and Whelan, R. F. (1954). *J. Physiol. (Lond.)*, **123**, 443.
Beattie, J. W., and Woodmansey, A. (1953). *Annals of the Rheumatic Diseases*, **12**, 43.
Catchpole, B. N., and Jepson, R. P. (1954). *Circulation*, **9**, 408.
Hatfield, H. S. (1950). *J. Physiol. (Lond.)*, **111**, 10*P*.
Hines, E. A., Wakim, K. G., Roth, G. M., and Kierland, R. R. (1950). *J. Lab. clin. Med.*, **36**, 834.
Hollander, J. L., Stoner, E. K., Brown, E. M., and De Moor, P. (1951). *J. clin. Invest.*, **30**, 701.
Janus, O. (1952). Unpublished observations.
Pickering, G. W. (1933). *Brit. med. J.*, **2**, 1106.
Vulliamy, D. G. (1952). *Lancet*, **2**, 1248.
Woodmansey, A. (1951). *Annals of the Rheumatic Diseases*, **10**, 65.

Effet vasculaire périphérique de la cortisone dans l'arthrite rhumatismale, la sclérodermie et les affections apparentées

RÉSUMÉ

(1) On étudia la réaction vasculaire périphérique en mesurant le débit calorique au cours du traitement par la cortisone de peu de durée chez 22 malades atteints de maladie rhumatismale, de sclérodermie et d'autres syndromes apparentés dans lesquels le débit sanguin digital est réduit.

(2) Au cours du traitement par la cortisone on nota une augmentation appréciable du débit sanguin digital chez les malades qui éprouvèrent un soulagement de la douleur et de la rigidité articulaire et chez qui le temps de l'hyperémie réactive fut inférieur à 5 secondes.

(3) Le test différentiel d'agglutination des cellules de mouton fut positif chez quatorze sur les 22 malades étudiés, mais la présence d'un test positif ne fut pas associée particulièrement à une réaction symptomatique ou vasculaire favorable à la cortisone.

(4) Après l'arrêt du traitement par la cortisone le débit sanguin digital tombait généralement en dessous du niveau existant avant le traitement.

Efecto vascular periférico de la cortisona en la artritis reumatoide, esclerodermia y afecciones afines

SUMARIO

(1) Se estudió la reacción vascular periférica por el método calorimétrico en el curso del corto tratamiento con cortisona en 22 enfermos con artritis reumatoide, esclerodermia y otros síndromes afines en los cuales la corriente sanguínea está reducida.

(2) En el curso del tratamiento con cortisona se notó un aumento apreciable de la corriente sanguínea digital en los enfermos que sintieron un alivio del dolor y de la rigidez articular y en los cuales el tiempo de la hiperemia reactiva fué inferior a 5 segundos.

(3) El test diferencial de aglutinación de células de oveja fué positivo en catorce de los 22 enfermos estudiados, pero la presencia de un test positivo no fué especialmente asociada a una reacción sintomática o vascular favorable a la cortisona.

(4) Al retirar la cortisona la corriente sanguínea digital caía generalmente debajo del nivel de antes del tratamiento.

SUPPRESSIVE AS COMPARED WITH ANALGESIC HORMONAL THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS*

BY

LAURANCE W. KINSELL

Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, California

(RECEIVED FOR PUBLICATION AUGUST 3, 1954)

About 25 years ago, I first became vaguely aware of the existence of the adrenal cortex. During the intervening quarter century, if any one fact concerning this organ has impressed itself upon me, it is the ubiquitous nature of the participation of its secretions in cellular and extracellular metabolism. The adrenal hormones are concerned in carbohydrate, protein, fat, fluid, and electrolyte metabolism; in immunological processes, with particular reference to the inflammatory reaction; and in the functional activity of every system in the body, including the central nervous system.

Following the stimulating observations of Hench, Kendall, Slocumb, and Polley (1949), many of us who had had small amounts of corticotropin sitting on our laboratory shelves for months, without any brilliant ideas as to how to use it in human subjects, found ourselves besieged with appeals to administer this material to arthritics. As a result, for a certain time patients with sore joints tended to displace dwarfs and giants in the beds of many metabolic wards.

It is the working philosophy in our Institute to select for admission to our precious metabolic beds patients whom we can help and from whom we can learn. Accordingly, we admitted patients with severe but potentially reversible joint damage, who, in return for such help as we might be able to give them, were willing to put up with the inconveniences of tube feeding and frequent blood-lettings, as part of long-term studies designed to evaluate the effect of ACTH, cortisone, and later hydrocortisone, upon certain aspects of fat metabolism. In order to avoid changes of questionable magnitude in the chemical entities under study, quite intensive hormonal dosage was employed during these studies. With such dosage, in a clinical sense, two things became apparent:

(1) All evidence of activity of the arthritic process disappeared in a matter of days (and reappeared rapidly if the dosage was decreased too rapidly or discontinued).

(2) Specific dietary factors played a major role in determining whether the untoward effects of intensive dosage of the hormones would be present in minimal or maximal degree. Specifically, it became increasingly clear that if large amounts of the hormones were to be administered, diets high in protein, high in potassium, adequate in calories, and low in sodium and carbohydrate, were mandatory. The reasons for administering protein and potassium and withholding sodium are readily explained. The basis for the increased incidence of Cushingoid manifestations with increase of dietary carbohydrate is still by no means clear. On the basis of clinical observation, however, a cause-and-effect relationship appears to exist.

Having instituted hormonal therapy in a group of arthritic patients, we were committed, insofar as we were able, to maintain them on a therapeutic programme compatible with maximal usefulness to themselves and to the community. Also, with the progress of months, we were faced with a significant number of patients with severe, but potentially reversible, joint damage, who could not be admitted to the metabolic ward. Having started with intensive or, if you will, completely suppressive therapy for the reasons noted above, we decided to continue it with these patients whom we accepted primarily for treatment, rather than for controlled metabolic studies.

Material

The observations which follow are derived from a total of 54 patients, all with severe rheumatoid arthritis (except as noted below), and potentially "salvageable".

* Presented by invitation at the annual meeting of the American Rheumatism Association, San Francisco, June 18, 1954. See p. 354.

This work has been supported in part by grants from the Armour Laboratories and Merck and Company. It was carried out in association with members of the Institute for Metabolic Research including Harry E. Balch, Nadine Foreman, Marjorie Coelho, and Florence Olson.

Grateful acknowledgement is made to the Armour Laboratories for supplies of ACTH; to Merck and Company for supplies of cortisone and hydrocortisone; and to the Schering Corporation for supplies of oestrogen and testosterone.

The Table summarizes the treatment given and complications encountered. As indicated, some have been under continuous treatment since 1950. One fact stands out most prominently: in not one patient have we been able to discontinue hormonal therapy completely.

TABLE

SUMMARY OF OBSERVATIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED SINCE 1950

(Mean duration of therapy 16 months)

Number of Patients	Total Patients		54	
	"Suppressive" Hormonal Therapy		37	
	"Analgesic" Hormonal Therapy		11	17*
	Hormonal Therapy was discontinued		6	
Reasons for Other than "Suppressive" Therapy	Psychosis		8	17*
	Alarming Gastro-intestinal Symptoms		7	
	Other		2	
Maintenance Dosage	Hormone	ACTH (units)	Cortisone (mg.)	
	Average	6	40	
	Maximum	40	150	
	Minimum	—	25	
Other Complications	Recurrent Exacerbations while on Therapy		4	7
	Late Complications		3	

* In these seventeen patients (of the original 54), it became apparent during the first few days or weeks of treatment that large dosage hormonal therapy would not be tolerated. Accordingly, they were placed on "analgesic" or no hormonal therapy as indicated in each individual case.

Results

Before going into specific problems encountered in a few selected patients, I should like to consider with you some general observations:

(1) In approximately three of every ten patients, intensive hormonal therapy proved to be impossible, for one or both of two reasons:

(*a*) Mental aberration.

(*b*) Abdominal discomfort of more than minimal degree.

Of the total number of arthritics whom we have seen the pattern of therapy has been changed from a suppressive to an analgesic variety in eleven, and hormonal therapy has been stopped in six.

(2) In a small group of patients Cushingoid manifestations appeared despite excellent adherence to diet. In some of them, the difference between 500 and 200 mg. sodium per day is critical. A constant diet containing less than 200 mg. sodium is unattractive to say the least. The administration of very large amounts of potassium (20 to 40 g. potassium chloride daily) may permit of a larger sodium intake in some; in others mercurial diuretics, in conjunction with high potassium intake, may be necessary.

(3) One may set up a reasonably sound "standard" programme for *initial* therapy of these patients, as follows:

(*a*) Hospitalization for a period of 10 days to 2 weeks.

(*b*) Hormonal therapy of sufficient intensity during the first week to bring the sedimentation rate to normal and to cause a disappearance of all pain and swelling in the involved joints.

(*c*) Progressive decrease in dosage during the remaining period of hospitalization to an amount compatible with the maintenance of a complete clinical remission.

(*d*) During hospitalization, the patient receives full instruction in the principles and practice of diet and medication.

(4) The establishment of a standard pattern of dosage for *long-term* maintenance is by no means absolute. Two individuals, each having arthritis of apparently equal severity, may have dosage requirements which vary by as much as 300 to 400 per cent. by the end of the second month of treatment. An average programme is shown in the Figure (opposite).

(5) The majority of patients who are likely to develop mental or gastro-intestinal difficulties will do so during the period of initial intensive hormonal therapy. Hence, during their period of hospitalization, it may be decided whether minimal analgesic therapy or no hormonal therapy is to be used. An occasional patient will do well during the hospital period, and then run into serious difficulty a few weeks or even a few months later. It is our impression that in at least some of these individuals, the appearance of mental, gastro-intestinal, or severe Cushingoid manifestations is referable to a break in the programme of adherence to diet.

(6) Oestrogen and/or testosterone may be of real value in the total programme. This applies particularly to menopausal women and elderly men. Inhibition of ovulation with oestrogen may prevent extreme accentuation of salt and water retention in the late progestational phase of the menstrual cycle.

Specific Cases

The two following cases represent the best and the worst results achieved in this series of patients.

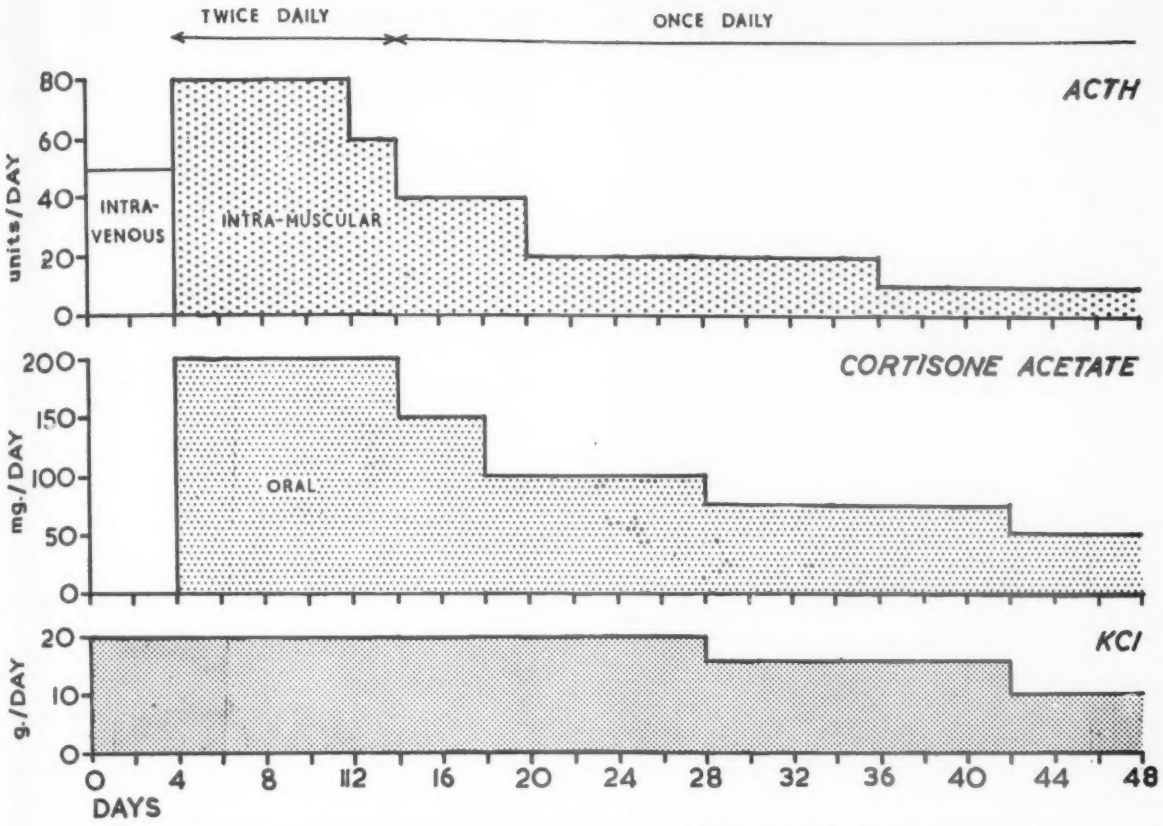


Figure.—Early part of programme reasonably constant in most patients, but late portion varies greatly.

Case 1, a man aged 20, was one of the relatively early patients, having been admitted to the metabolic ward in August, 1950. He was the first individual in whom it was clearly obvious that changes in diet produced major modification of clinical and metabolic patterns during hormone administration (Kinsell and others, 1952). At the time of admission, he was so crippled as to be unable to continue with his classes at the university. During a prolonged period of intensive hormonal administration, on a diet containing large amounts of fat and inadequate amounts of protein, he developed a severe pneumonitis, from which he recovered slowly. He was discharged from the metabolic ward in October, 1951, on a dosage of 37·5 mg. cortisone daily. After discharge he was able to take a part-time and eventually a full-time post as a draughtsman. At the present time, 4 years after the institution of therapy, his programme is college half-time, and work half-time, on a maintenance dosage of 25 mg. cortisone daily. Attempts to reduce the dosage below this level have been associated with the reappearance of joint symptoms.

Case 2, a woman aged 37, was first seen by us in May, 1952, at which time she had severe widespread arthritis, and severe unilateral iridocyclitis. Since then, she has been hospitalized five times. On two occasions, hundreds of units of intravenous ACTH and thousands of milligrams of cortisone or hydrocortisone have been required to bring her eye and joint manifestations under control. On several occasions this large dosage has been associated with significant disorientation, but fortunately this has been transient. If her problem had been one of joint involvement alone, we should probably have discontinued hormonal therapy, but to do so would almost certainly have resulted in the loss of one or both eyes.*

Fortunately, few individuals present as difficult a problem as the latter patient, but most require larger maintenance dosage than Case 1. The trend of dosage in the majority, however, is steadily downward. It is usually found that those whose dosage requirements continue high have failed to adhere to the prescribed programme of adequate rest and exercise, proper diet, and avoidance of emotional trauma.

* Since this was written, the patient has had a psychotic episode during very intensive hormonal therapy for an acute exacerbation, and hormonal therapy was stopped on June 8, 1954. There has since been no evidence of active arthritis or iridocyclitis up to the present time (September 19, 1954).

Experience with Other Forms of "Collagen Disease"

It has also been attempted to attain complete suppression of disease in cases of lupus erythematosus, polyvasculitis, dermatomyositis, scleroderma, pemphigus, and rheumatic fever.

Pemphigus.—In the first patient so treated, a woman aged 46, who was in a near moribund condition after a year of steady progression of the disease, treatment was continued for more than a year in gradually decreasing amounts. She has been off all therapy for more than 2 years, and appears to be perfectly well.

Dermatomyositis.—The first patient, a woman aged 43, has been under continuous treatment since 1949; it has not been possible for her or any other patient in our small series to discontinue therapy, but the maintenance levels tend to be rather small.

Polyvasculitis.—Long-term complete suppression of the disease has not been achieved in any patient, but suppressive therapy of a magnitude compatible with full or nearly full activity has been possible in several.

Scleroderma.—The results were similar to the foregoing.

Lupus Erythematosus.—Almost without exception, a large dosage of the hormones has been necessary not only to produce but to maintain a reasonable degree of remission. Some patients have shown a remarkable tolerance for continued high dosages.

Rheumatic Fever.—All patients with an initial severe attack, having clinical or electrocardiographic evidence of carditis, are treated with sufficient amounts of ACTH and cortisone to bring down the sedimentation rate to normal levels, the objective being to protect the heart until the major force of the particular attack has spent itself. Treatment is decreased and discontinued as soon as feasible, usually in 3 to 4 weeks. The majority of patients who have had several attacks of the disease are treated only with aspirin and rest in bed. We are not at all certain that we have yet found the best approach to the problem.

Discussion

In a patient with rheumatoid arthritis, one may follow one of at least four courses insofar as hormonal therapy is concerned:

(1) No hormonal therapy whatever.

(2) A relaxed approach, with no attempt at regulating diet or other adjuvant measures, the patient being advised to "take one or several cortisone tablets when your joints hurt".

(3) A carefully regulated programme of diet and other measures, using minimal hormonal therapy in conjunction with aspirin and other analgesics, designed to maintain a state of reasonable control.

(4) A programme of completely suppressive therapy, such as is outlined above.

All serious students of arthritis, and all who are interested in the use of the corticoids, will agree that the second procedure is to be avoided at all costs, but at that point agreement stops.

It seems to us better to treat arthritics with corticoids than to withhold such therapy, so long as both patient and physician are acutely aware of two important facts:

(1) Hormonal therapy is in no sense the final answer to the disease;

(2) Such therapy carries with it the very real possibility of certain untoward side-effects.

That we have chosen to use more intensive (suppressive) hormonal therapy than is advised by most workers, is probably attributable to the fact that we approached rheumatoid arthritis by way of a primary interest in the metabolic effects of hormones, instead of approaching the hormones by way of a primary interest in arthritis.

The objective of all those who are concerned in treating arthritic patients is to "hold the line" as best we can until the final answers regarding cause and cure of the disease are found. Our definition of "holding the line" would be:

(*a*) Prevention of further joint damage;
(*b*) Restoration to a useful status;
(*c*) Avoidance of therapy which superimposes serious iatrogenic pathology upon the original arthritis.

Those who continue to rely entirely upon rest, physiotherapy, and aspirin, avoiding hormonal therapy, do so because of their serious concern regarding the untoward effects of the latter.

Most of those who use the lowest hormonal dosage compatible with a fair degree of comfort and decrease in joint inflammation, do so because of their concern about the short-term and long-term untoward side-effects of a larger dosage.

Those who use completely suppressive hormonal therapy, do so for the following reasons:

(1) With proper attention to diet and other adjuvant measures, the occurrence of untoward side-effects will probably be no greater than with the lower dosages required in analgesic hormonal therapy.

(2) The net amount of hormones administered over a period of 2 or more years will probably be no greater than that used in the analgesic programme.

(3) The net salvage of patients is significantly greater than can be achieved by the analgesic approach.

More than 90 per cent. of the patients included in this report had "severe" arthritis, and there is not a "mild" case among them. Several of those who made a satisfactory response, had been considered as failures in terms of response to "analgesic" hormonal therapy. Several of our rheumatologist friends have been disturbed, because so far we have been unable to discontinue therapy in *any* patient, but the severity of the disease in this series of patients may be the explanation.

Summary

Suppressive hormonal therapy in 54 patients with severe rheumatoid arthritis was carried out for 4 years. On the basis of the experience gained it seems probable that:

(1) The "net salvage rate" of such patients is higher than could be achieved by the use of analgesic hormonal therapy.

(2) The total dosage of hormones over a period of 2 or more years, and the incidence of complications, is probably no greater than that observed with the analgesic approach, assuming that meticulous attention is paid to diet and other adjuvant measures.

REFERENCES

Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, **24**, 181.

Kinsell, L. W., Partridge, J., Boling, L., Margen, S., and Michaels, G. (1952). *J. clin. Endocrinol.*, **12**, 909.

Thérapie hormonale répressive comparée a l'analgésique des rhumatisants arthritiques

RÉSUMÉ

La thérapie hormonale répressive fut appliquée pendant 4 ans à 54 malades atteints d'arthrite rhumatismale grave. Selon l'expérience gagnée, il semble probable que:

(1) Le "pourcentage net de sauvetage" de tels malades est supérieur à celui qu'on pourrait obtenir par le traitement hormonal analgésique.

(2) La quantité totale d'hormones administrée pendant deux ans ou plus, ainsi que la fréquence des réactions secondaires ne sont probablement pas plus grandes qu'avec la méthode analgésique, pourvu que le régime alimentaire et les mesures adjuvantes soient l'objet des soins méticuleux.

Terapia hormonal supresora comparada con la analgésica en enfermos con artritis reumatoide

SUMARIO

Cincuenta y cuatro enfermos con artritis reumatoide fueron sometidos durante 4 años a la terapia hormonal supresora. A base de la experiencia ganada parece probable que:

(1) La "proporción neta de salvamento" de tales enfermos es superior a la que se pudiera alcanzar por la terapia hormonal analgésica.

(2) La cantidad total de hormonas administrada durante dos años o más, así como la frecuencia de fenómenos secundarios no exceden probablementes las observadas con el empleo del sistema analgésico, provisto que se ponga atención meticulosa en el régimen alimenticio y las medidas coadyuvantes.

PSYCHO-SOCIAL FACTORS IN REHABILITATION OF THE CHRONIC RHEUMATOID ARTHRITIC*

BY

EDWARD W. LOWMAN, SAUL MILLER, PHILIP R. LEE, HARRY STEIN, REVA KING, and LILLIAN HEALD

From the Departments of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Centre and Goldwater Memorial Hospital, New York City

(RECEIVED FOR PUBLICATION SEPTEMBER 6, 1954)

For the past two years we have engaged in a research project devoted to the problems of rehabilitation among chronically disabled rheumatoid arthritis patients. To be admitted to the study, patients had to be severely disabled, and their disease process had to be still in an active phase. Our objective was to determine the feasibility of a combined programme of hormone therapy and physical medicine rehabilitation procedures. Previous papers (Rusk and Lowman, 1953; Lowman and Lee, 1953; Lowman, 1953) have reported the factors considered most important in establishing and attaining goals with such chronic arthritis patients; among these, the psycho-social aspects of the problem were prominent.

Many writers support the hypothesis that the psychological status of the rheumatoid arthritic warrants consideration as specific to this disease. Some investigators have proposed that this "rheumatoid personality" is a stigma which antecedes the disease and predisposes psychosomatically to its development as a clinical entity (Johnson and others, 1947; Rome, 1949; Halliday, 1944; Ludwig, 1952, 1954). We have looked out for any personality structure characteristic of arthritics and its influence on the possibilities of rehabilitation. We have also tried to distinguish the motivated from the non-motivated patient, since rehabilitation is a protracted and expensive treatment. We have previously reported the high incidence of passivity and dependence in the chronic rheumatoid group, and in analysing our patients from a psycho-social standpoint, we have looked for characteristics among the successful and unsuccessful groups of rehabilitees which could be used as yardsticks in selecting those patients for rehabilitation who will be most likely to derive benefit from the treatment.

Method of Study

In the first year of this study, 239 candidates for treatment were referred to us. From this large group, 37 were selected for special analysis as they fulfilled the criteria of being both severely disabled and still in the active phase of the disease. These 37 patients were hospitalized and treated by a staff devoted full-time to the study, and the psycho-social data used was obtained during hospitalization. Initially, each patient was seen by both the psychologist and the social worker. During the social worker's initial interview, a comprehensive history was obtained of psycho-social development from early childhood to the onset of the arthritis, and subsequent adjustments to the illness. The psychologist's initial evaluation was based on such psychological tests as the Wechsler-Bellevue; on projective tests, including Thematic Apperception, Rorschach Ink Blot, and Figure Drawing; and on vocational tests, such as Kuder Preference, Purdue Pegboard, and others as indicated.

With this initial data, the social worker and the psychologist discussed the patient's problems from a psycho-social standpoint with the psychiatrist, and from this conference a plan for subsequent rehabilitation was formulated. The plan for treatment depended upon the patient's capacity and desire for developing and utilizing insight, his quality of adjustment, and the nature of his environmental, social, and emotional problems. These initial decisions were subject to review during hospitalization, and weekly staff meetings were held to co-ordinate reports on behaviour and progress.

Social and Psychological Features of the Group

Before taking the patients separately, it is important to consider the descriptive analysis of the larger patient population with which we have been dealing. A detailed analysis was made for the first 29 patients.

Sex.—Thirteen were males and sixteen females.

Mean Age.—47 years.

Age at Onset of Arthritis.—The mean was 36 years (ranging from under 20 to over 45).

Marital Status.—Of the 29 patients, only ten were still married; this is less than would be expected for this age group and indicates the presence of problems of heterosexual adjustment. Almost 50 per cent. of the patients had restricted heterosexual relationships, and were frequently fearful, and distrustful of persons of the opposite sex. One-third of the patients had never married, and for only one-third was the marriage permanent. Although death was a rather frequent reason for

* This study is being supported by a grant from the United States Public Health Service.
Merck and Company have generously assisted by supplying Cortone.

termination of marriage, this had occurred in all cases within a few years of marriage and was so early that remarriage might have been anticipated. Either overt or covert conflict in the marital relationship was extremely prevalent; at most, only three marriages seemed to involve no more than the reasonable amount of conflict. Two-thirds of the patients did not want children and among those who expressed a desire for children the expression was frequently marked with ambivalence with rarely a positive interest.

Racial and Cultural Background.—Of the 29 patients, 25 were white and 4 were Negroes. Only seven were of second generation or longer descent, the rest being either first generation Americans or foreign born, so that the group does not represent a normal population with respect to nationality. The significance of this can only be speculative, but some of their problems were related to difficulties in cultural adaptation.

Religious Background.—The group was not typical of a normal population, two-thirds being Catholics. Irrespective of religious denomination, a rigid religious training seemed to be a significant factor, twelve of the 29 patients (nine Catholics and three Protestants) having been brought up in homes with strict religious adherence.

Economic Background.—This compared closely with that of a normal population; the majority of the patients had accomplished only a poor or fair standard of living, but this was due to the handicap of poor health and could not be considered significant. Most of the patients had not qualified for any particular trade or profession, but one-half of them had relatively stable work histories.

Family Background.—Here the most outstanding feature was the high incidence of changes in family structure. For only nine of the 29 patients did the family structure remain stable throughout early childhood. One-half of the patients were separated from at least one parent because of death or for some other reason before they were 7 years old, and most of them had to make subsequent adjustments following the remarriage of parents, etc. The predominant influences on personality development had been negative. In 22 out of the 29 cases, the maternal attitude appeared to have been predominantly negative, and for 21 of the patients the paternal attitude was a negative one. Most frequently the mothers had been dominating and controlling, and the fathers passive, ineffectual, disinterested, and seldom available.

The relationship of the patient with his siblings was often one of competition and jealousy, with associated feelings of inferiority characteristic of sibling rivalry (observed in thirteen out of 29 cases). Only three patients gave histories indicative of healthy relationships among siblings.

Educational Background.—Here the patients compared closely with the general population. Only six completed high school or higher education. The major reason for terminating schooling was lack of interest or effort in continuing schooling after starting employment.

Among early childhood interests, physical activities were predominant and were emphasized by twelve of the 29 patients. Success in competitive sports was described by several of the patients.

Precipitating Factors of Disease.—The patients attributed their illness to a variety of causes, but most often related it to other health problems or to environmental factors, such as poor working conditions, over-exertion, accident, tight shoes, etc. Most patients did not spontaneously refer to emotional traumata, but in discussing life histories a chronological relationship of such traumata was frequently noted. Among twelve of the patients, serious illness, death, or separation from an immediate family member occurred just before the onset of the disease. In five patients the arthritis followed childbirth or began concurrently with the responsibilities of child care, and in three others it developed at the time they became engaged or just after marriage. Several patients described conflicts with authority (employers, etc.) just before the onset of arthritis. Evaluation of the possible relationship between onset of disease and emotional trauma presents many difficulties. The patients frequently did not consider these experiences to be traumatic, but in their total histories their evaluation of emotional strains frequently indicated similar omissions, repressions, or confusion, so that no valid conclusions could be drawn regarding the chronological relationship between emotional stress and the onset of arthritis.

Psycho-Social Consequences of Illness.—The development of the arthritis in these patients caused changes in nearly every area of life, from employment to recreational activities; 21 of the 29 patients were employed at least part-time at the onset of the arthritis, and all these had been financially dependent for at least one year prior to admission to the research project. Increased social dependence most frequently was reported by patients in describing changes in their social situations. Only three patients reported an unaltered dependency status; these were patients who refused to ask for help from relatives, or who had no families to which to turn.

The two other most common areas of change were in family roles and extra-curricular activities. The latter change might have been expected in higher incidence except that many of the patients had no outside interests for curtailment. The shift in family role took the form of relinquishing of the care of children to relatives, moving the parents' home, and in other social adjustments necessitated by the illness.

In nearly every instance the illness functioned as a defence for the patient against his environment, by providing a punishment of self or family, a means of enforcing environmental control, or a means of establishing or justifying dependence. For several patients the arthritis provided a satisfactory excuse for his withdrawal from the environment and an adequate rationalization for his feelings of inadequacy. The implications of these defences and the need for illness were manifold, and were of paramount influence in rehabilitation progress. For some patients their "ego strength" was sufficient to minimize their need for such a self-destructive defence, but for others the environment was too threatening to permit the surrender of illness.

Preliminary Results

From the 29 hospitalized patients, six failures and six successful rehabilitees were selected. The data on these twelve patients were then analysed in greater detail in the hope of establishing common denominators which might serve as positive and negative indicators (Tables I-III). By definition, the successful rehabilitee was one who was able to utilize his remaining physical resources to a reasonable degree. Conversely, the failure was able to use few or none of his physical resources and made little or no attempt towards self care and independent living. With one exception, all these cases had been under observation for from 6 to 12 months. Patients not clearly classifiable as successful or unsuccessful were not included, but are now subjects for testing the hypotheses developed by this comparative analysis.

The results are of necessity preliminary ones since this research project has now completed only two years of its projected 5-year course.

Summary and Conclusions

On the basis of the psycho-social data so far accumulated, it may be said tentatively that the most successful chronic rheumatoid arthritic rehabilitee was a second-generation American, of poor socio-economic status, and of moderate religious practice. He was capable of handling heterosexual conflicts, and of taking decisive action in terminating the relationship in situations of marital discord. He began work early without direct pressure and maintained a good work history. Economically, he attained a fair or reasonable standard of living, superior to that of his early family status, and maintained his home independently with his spouse. Financially, he was independent for at least 5 years before the onset of his illness. The median length of illness and the median age at onset of illness were similar to those of the unsuccessful rehabilitee, but there was a greater variability in both duration of illness and age at onset among successful rehabilitees.

TABLE I
SOCIAL BACKGROUND

Life History		Successful	Unsuccessful
Early Family Background	Birthplace	2nd-generation American or more	1st-generation American or foreign-born
	Socio-economic Status	"Poor" early background	"Fair" or "good"
	Religious Training	Moderate religious practices	Strict religious practices
Adult Social Adjustment (heterosexual adjustment)	Age began "Dating"	Mid or late 'teens	Early 'teens or after age 20
	Nature of Marital Relationship	No present marital conflict; either terminated unsatisfactory marriage or did not marry	Marked marital conflict with inability to resolve or terminate unsatisfactory marriage
	Age at Marriage	If married, marriage at reasonable age (19 to 25 yrs)	Marriage outside usual age range —premature or delayed
Education and Work	First Employment	Began work in 'teens; little direct pressure to begin work and no pressure against working	Delayed employment (after age 20) some with pressure against working, and others with great pressure to begin working
	Adult Economic Achievement	Maintained "fair" or reasonable standard of living	"Poor" standard of living
	Changes in Economic Situation from Early Childhood	Attained status superior to early family economic status; no decline	Remained the same or declined
Situation before Illness	Financial Independence: (no essential difference in occupation between groups)	Financially independent for 5 years before onset (except two who were under working age for part or all of 5 years before onset)	Most wholly or partly financially dependent
	Living Arrangements	Maintaining home independently or with spouse (two were 20 years or younger at onset and were in parental home)	Half failed to establish independence
	Patient's Evaluation of Health before Onset (covering previous 10-15 yrs)	Good physical condition and functioning well	Most considered themselves "poor" or only "fair"

The disability of the successful rehabilitee was generally less severe. His attitude towards his illness was one of acceptance of life within limitations but with maximum function and without undue conflict. His goal in rehabilitation, in contrast to the vague, confused, unrealistic aims of the unsuccessful candidate, was usually specific and realistic. His use of the psycho-social department in the hospital tended to be more for control of environment and development of insight. His hypochondria was of only moderate degree, and his passivity and acceptance was associated with fear

TABLE II

PSYCHOLOGICAL CHARACTERISTICS

Psychology		Successful	Unsuccessful
Verbal Intelligence		Low-average (or better)	Borderline
Ego Strength		More adequate	Less adequate
Control	Emotions	Control and/or repression of emotional reactions	Uncontrolled emotional reactions; impulsivity and egocentricity
	Fantasies	Control and/or repression of fantasies	Fearful, uncontrolled fantasies
	Depression	Desire and capacity for pleasurable experiences far outweighing depressive mood	Depressed mood tends to obscure and displace pleasurable experiences, resulting in chronic depressive mood
	Orality	Little evidence of oral concern	Strong oral needs concerned with food and drink; chronic feelings of failure to achieve oral gratification
	Body image	Relatively adequate body image; adequate differentiation of parts, presence of all extremities, adequate size	Inadequate, distorted, bizarre body image; frequent lack of differentiation, missing parts of body, poor line

TABLE III

PROGRESS IN REHABILITATION

	Patient's Reactions	Successful	Unsuccessful
Attitude to Rehabilitation (Aims)	Non-specific, vague, confused or inconsistent aims	2	4
	Specific, but not realistic	—	2
	Specific and realistic	4	—
	Nil	—	—
Attitude to Illness (including disfigurement)	Acceptance by adapting to life within limitations, but with maximum function and without undue conflict	4	—
	Acceptance of chronic invalidism as a way of life providing some satisfactions, no apparent conflict or need for change	—	3
	Resignation with little or no hope of improvement but some conflict over adopting chronic invalidism as a way of life	1	1
	Non-acceptance, marked depression, embarrassment by helplessness or disfigurement	1	—
	Non-acceptance, denial of reality, waiting on miracle, and determined to achieve complete recovery	—	2
Attitude to Dependency	Aggressive and demanding, with no manifest conflicts	—	1
	Aggressive and demanding or assertive, with conscious conflict as indicated by alternating periods of aggression, denial of needs for help, etc.	—	3
	Passive acceptance with no manifest conflict	1	1
	Passive acceptance, with some apparent conflict, fears, asking for help, etc.	5	1
Attitude to Use of Psycho-Social Service	Resentment of interest and/or denial of any problems and/or fear of attempts at understanding	1	1
	No interest or passive acceptance	—	1
	Acceptance of control of environment (including help with environmental problems)	4	5
	Acceptance of emotional support	1	2
	Acceptance of help in development of insight	3	1
Degree of Hypochondria	Extensive emphasis on complaints	—	2
	Moderate	2	2
	Limited	4	1
	Undetermined	—	1
Degree of Responsibility and Participation in Treatment	Little or none	—	4
	Limited to fair	3	2
	Moderate to good	1	—
	Excellent	2	—

and reluctance to ask help from others, whereas the unsuccessful rehabilitee was full of hypochondriacal complaints and was aggressive and demanding in his reaction to dependency. Psychologically, the successful patient was of low-average (or better) verbal intelligence with adequate "ego strength"; he showed control and/or repression of his emotional and imaginative experience, and his desire and capacity for pleasurable experiences outweighed his depressive moods. There was relatively little oral need, and an adequate body image, without distortion or bizarre interpretation.

The unsuccessful candidate showed the opposite of these psycho-social features to such an extent that we now feel the above to be possible criteria for assessing which chronic arthritics may be good risks for acceptance into the rehabilitation groups, and we have now decided to select on this basis.

REFERENCES

Halliday, J. L. (1944). *Practitioner*, **152**, 6.
Johnson, A., Shapiro, L. B., and Alexander, F. (1947). *Psychosom. Med.*, **9**, 295.
Lowman, E. W. (1953). *Industr. Med. Surg.*, **22**, 304.
——, and Lee, P. (1953). *Arch. phys. Med.*, **34**, 175.
Ludwig, A. O. (1952). *Bull. rheum. Dis.*, **2**, no. 8, p. 15.
—— (1954). Unpublished data.
Rome, H. P. (1949). *Med. Clin. N. Amer.*, **33**, 1061.
Rusk, H. A., and Lowman, E. W. (1953). Proceedings of the Eighth International Congress of Rheumatic Diseases. Geneva. In the press.

Les facteurs psycho-sociaux dans la réhabilitation du rhumatisant arthritique chronique

RÉSUMÉ ET CONCLUSIONS

En se basant sur les données psycho-sociales accumulées jusqu'à présent, on peut dire tentativement que le meilleur candidat à la réhabilitation parmi les rhumatisants arthritiques chroniques est un Américain de deuxième génération, d'un milieu social et économique pauvre qui pratique sa réligion avec modération. Il est capable de manier les conflits hétérosexuels et de prendre des mesures décisives dans les situations de désaccord matrimonial en terminant le rapport. Il a commencé à travailler de bonheur et son passé de travail est bon. Economiquement, il a atteint un niveau de vie bon ou raisonnable, supérieur à celui qu'il avait connu dans sa famille et il a maintenu son foyer indépendamment avec son épouse. Matériellement il était indépendant pendant 5 ans au moins avant le début de sa maladie. La durée moyenne de la maladie et l'âge moyen de son début sont similaires pour le candidat échoué, mais parmi les réussis la variabilité est plus grande aussi bien en ce qui concerne la durée que l'âge de début de la maladie.

L'infirmité du candidat réussi était généralement moins sévère. Son attitude à l'égard de sa maladie était celle d'acceptation de la vie avec ses limitations mais avec un maximum de fonction et un minimum de conflit peu justifié. L'objet de sa réhabilitation, contrairement aux buts vagues, confus et irréels du candidat échoué, était généralement spécifique et réaliste. Il tendait à se servir du department psycho-social de l'hôpital plutôt pour contrôler le milieu ambiant et développer sa perspicacité. Son hypochondrie n'était que modérée et sa passivité et acceptation était associée à la peur et répugnance de demander sécours aux autres, tandis que le candidat échoué ne cessait pas de se plaindre et était agressif et exigeant dans sa réaction à la dépendance. Du point de vue psychologique, le malade réussi avait une intelligence verbale basse-moyenne (ou mieux) avec la "force de l'ego" suffisante; il contrôlait et/ou reprimait son expérience émotive et imaginative et son désir et sa capacité d'éprouver des expériences agréables l'emportaient sur les tendences dépressives. Ses besoins buccaux étaient relativement petits, et son image corporel adéquat, sans distorsion ni interprétation bizarre.

Le candidat échoué montrait des traits psychosociaux contraires à tel point que maintenant nous croyons que les critères ci-dessus peuvent servir pour déterminer lequel des arthritiques chroniques est un bon risque pour l'admettre au groupe de réhabilitation et nous venons de décider de nous baser la-dessus pour la sélection.

Los factores sico-sociales en la rehabilitación del enfermo con artritis reumatoide crónica

SUMARIO Y CONCLUSIONES

Basándose en los datos sico-sociales acumulados hasta ahora, se puede decir tentativamente que el mejor candidato a la rehabilitación entre los enfermos con artritis reumatoide crónica es un americano de segunda generación, de un medio social y económico pobre y moderadamente religioso. Sabe manejar los conflictos heterosexuales y en situaciones de desacuerdo matrimonial tomar acción decisiva rompiendo las relaciones. Empezó a trabajar temprano y tiene un buen pasado de trabajo. Económicamente alcanzó un nivel de vida buen o razonable, superior al nivel temprano de su familia y mantuvo su hogar independientemente con su esposa. Materialmente, fué independiente durante cinco años al menos antes del comienzo de su enfermedad. La duración media de la enfermedad y la edad media de su comienzo aseméjanse a las del candidato fracasado, pero entre los venturosos hay mayor variabilidad tanto respecto a la duración como a la edad de comienzo de la enfermedad.

La incapacidad del candidato venturoso fué generalmente menos grave. Su actitud hacia su enfermedad fué la de acepción de la vida con sus limitaciones pero con un máximo de función y un mínimo de conflicto indebido. El objeto de su rehabilitación, contrariamente a los propósitos vagos, confusos y poco reales del candidato fracasado, fué generalmente específico y realista. Tendió a servirse del departamento sico-social del hospital más bien para controlar el medio ambiente y para desarrollar su percepción. Su hipocondria fué moderada y su pasividad y acepción fueron asociadas con un temor y una repugnancia de pedir ayuda de los demás, mientras que el candidato fracasado no acabó de quejarse y fué agresivo y exigente en su reacción a la dependencia. Sicológicamente, el venturoso tuvo una inteligencia verbal baja-media (o mejor) con la "fuerza del ego" suficiente; supo controlar y/o reprimir su experiencia emotiva e imaginativa y su deseo y su capacidad de experiencias agradables preponderó sobre sus tendencias depresivas. Su necesidad oral fué relativamente poca, su imagen del cuerpo adecuado, sin perversión o interpretación grotesca.

El candidato fracasado mostraba rasgos sico-sociales opuestos a tal punto que ahora pensamos que los criterios enumerados pueden servir para determinar cual de los artríticos crónicos presenta un buen riesgo para su admisión al grupo de rehabilitación y ahora hemos decidido de basarnos en ello para la selección.

METABOLIC EFFECT OF PHENYLBUTAZONE IN GOUTY AND NON-GOUTY ARTHRITIS*†

BY

E. R. HUFFMAN, G. M. WILSON, C. J. SMYTH, and R. HILL

From the Departments of Medicine and Biochemistry, University of Colorado, and the Veterans Administration Hospital, Denver, Colorado

(RECEIVED FOR PUBLICATION SEPTEMBER 6, 1954)

Phenylbutazone ("Butazolidin") is an effective therapeutic agent in acute gouty arthritis (Kuzell and co-workers, 1952, 1954; Kidd, Boyce, and Freyberg, 1952, 1953; Stephens, Yeoman, Holbrook, Hill, and Goodin, 1952; Steinbrocker, Berkowitz, Ehrlich, Elkind, and Carp, 1952; Engleman, Krupp, Forsham, Griffin, Johnson, Green, and Goldfien, 1953). It is a synthetic pyrazol derivative, with the chemical designation 3,5-dioxo-1,2-diphenyl-4-n-butylpyrazolidine. In this clinic, 21 patients with 29 acute episodes of gouty arthritis have been treated with oral doses of 100 or 200 mg. phenylbutazone 4-hrly. In every instance all joint discomfort was controlled within 24 to 48 hrs and most of the attacks were aborted in 8 to 12 hrs.

Although phenylbutazone has been shown to be an effective therapeutic agent in gouty arthritis, and its effectiveness has been associated with a fall in the serum level of urate, there has been disagreement regarding the explanation for this phenomenon. Kuzell and others (1952, 1954) and Kidd and others (1953) have reported that the drug has no effect on the excretion of urate. Johnson and others (1954) studied two patients under therapy for periods of 4 days and noted a fall in the serum urate concentration with a reduction in the urine urate. Mason (1954) reported that phenylbutazone had a uricosuric effect in three out of four cases of gout and in one subject with Paget's disease of the bone. In our experience, phenylbutazone causes an increase in urate excretion. The observations which form the basis for this report are in agreement with those of Yü, Sirota, and Gutman (1953), who demonstrated a definite increase in the renal clearance of urate in gouty subjects during short-term infusion experiments as well as an increased 24-hr urinary urate excretion after oral administration of phenylbutazone.

It has been noted that in gouty patients the elevated plasma urate level generally falls to normal or almost normal shortly after the administration of phenylbutazone. Kidd and others (1952) determined the change in the plasma urate values in fifteen patients with gout and found the average decrease to be 3·5 mg. per cent.; in thirteen non-gouty patients who had been receiving phenylbutazone, the average decrease was 1·2 mg. per cent. The mechanism of this decrease was not established. Kuzell and others (1952, 1954) state that, although the uric acid values in the serum promptly fell after the use of phenylbutazone, there was no consistent increase in the urinary excretion coincident with decrease in serum uric acid. Kidd and others (1952), in a study of nine patients with uncontrolled diets, observed no significant increase in output of urinary urate, they suggested that the decrease in plasma concentration of uric acid may not be due to a uricosuric action of this drug. In preliminary studies reported from this laboratory (Smyth, 1953; Huffman and others, 1953) results were obtained contrary to these observations.

Methods

It was the purpose of this study to obtain information on the effect of phenylbutazone on the serum urate levels and the 24-hr excretion of urinary urate. The uricosuric effect of different serum levels of this drug administered orally was determined.

Daily serum and urinary uric acid levels were determined according to the method reported by Forsham and others (1948). Aliquots of the 24-hr urine were extracted with ethyl ether before the urate determinations were made. Completeness of collection of 24-hr urine specimens was checked with creatinine determinations. All of the patients were on a constant low purine diet containing 50 g. protein. Serial phenylbutazone blood level

* These studies were aided by grants from the Rocky Mountain Chapter of the Arthritis and Rheumatism Foundation and the Geigy Pharmaceuticals, Inc., New York, New York. Based in part on a thesis submitted by Dr. G. M. Wilson, Jr., to the Faculty of the Graduate School of the University of Colorado in partial fulfilment for the degree of Master of Science in Medicine.

† Based on material presented in a discussion at the annual meeting of the American Rheumatism Association, June, 1954. See p. 366.

determinations were done, using the method of Burns and others (1953). The daily dose schedule was either 400, 600, 800, or 1,200 mg. per 24 hrs in divided dosage. Clearance studies, using simultaneous endogenous creatinine and urate determinations, were done on three gouty and five non-gouty subjects. Collection periods were of 20 minutes duration with bladder wash-outs. Creatinine determinations were made by the method of Bonsnes and Taussky (1945).

Results

Serum and Urinary Uric Acid Changes.—The effect of 8 days of oral administration of phenylbutazone on the serum urate and 24-hr urinary urate excretion in both gouty and non-gouty arthritics is shown in Table I. It is noteworthy that the serum urate decreased after therapy in all instances. The mean fall in the serum urate of the gouty patients was 3·6 mg. per cent. (44 per cent. of the mean control value), while the non-gouty patients had a mean fall in the serum urate of 2·4 mg. per cent. (42 per cent. of the mean control value). The average fall in the serum urate for doses of 600, 800, and 1,200 mg. per 24 hrs was 2·4, 3·8, and 3·2 mg. per cent. respectively. The average serum phenylbutazone levels for doses 600 and 800 mg. per 24 hrs were 14·3 and 15·4 mg. per cent. respectively. Serum drug levels were obtained only in two of the seven patients receiving the 1,200-mg. dosage.

The patients with gout showed a peak 24-hr increase in urinary urate excretion averaging 350 mg., while the non-gouty patients had a peak increase of 211 mg. The maximum rise in the urine urate in sixteen out of nineteen instances occurred before the serum urate reached its lowest level. One patient (Case 9) is of interest; while his serum uric acid *fell* slightly during therapy, the urinary excretion of uric acid showed no rise, in fact it decreased. This patient had marked hypertensive cardiovascular renal changes and while under study developed considerable oedema and other manifestations of fluid retention. Only one 24-hr urine urate in all the other gouty patients failed to exceed the control value.

The mean value of urinary urate excretion was determined in ten instances in seven gouty patients, and in nine instances in seven non-gouty patients (Table I). The gouty subjects showed a significant increase in urate excretion. This data was subjected to analysis by the *t*-test and found to be significant at less than the 2 per cent. level. The mean increase in the 24-hr urine urate excretion during the period of phenylbutazone administration was 204 mg. per

TABLE I

EFFECT OF DAILY ADMINISTRATION OF PHENYLBUTAZONE ON SERUM AND URINARY URIC ACID

Diagnosis	Case No.	Phenylbutazone		Serum Uric Acid		Urinary Uric Acid		
		Dose per 24 hrs (mg.)	Maximum Serum Level (mg./ml.)	Control (mg./ml.)	After Therapy (mg./ml.)†	Control (mg./24 hrs)	After Therapy (mg./24 hrs)†	Mean Excretion (mg./24 hrs)
Gouty	1	400	12·0	10·4	7·2 (8)‡	348	590 (6)‡	482
	2	600	14·5	7·0	2·8 (9)	334	792 (6)	577
	3	600	14·0	7·9	6·6 (5)	197	495 (4)	448
	2	800	15·2	7·5	3·1 (7)	450	752 (6)	657
	4	800	14·8	7·1	4·1 (8)	432	643 (2)	510
	5	800	15·7	7·8	3·8 (6)	*	*	
	6	800	14·2	9·5	3·8 *	354	807 *	
	7	1,200		8·2	4·4 (7)	303	879 (5)	617
	2	1,200		7·3	3·2 (5)	507	896 (2)	877
	1	1,200		7·9	4·5 (7)	349	728 (2)	639
	8	1,200		7·8	2·9 (9)	542	1,179 (4)	823
	9	1,200		10·1	9·5 (7)	425	324 (1)	292
Non-Gouty	10	400	9·0	5·6	4·3 (7)	650	891 (9)	672
	11	600	14·2	7·6	6·0 (8)	780	859 (7)	721
	12	600	16·1	4·7	2·8 (8)	453	596 (5)	528
	13	600	11·3	5·3	3·2 (7)	340	704 (4)	545
	14	600	15·6	7·1	3·6 (8)	760	1,069 (1)	817
	15	800	15·9	6·2	2·8 (7)	571	876 (5)	692
	10	800	16·9	5·4	3·0 (8)	650	864 (4)	768
	12	1,200	20·2	4·7	1·9 (6)	453	604 (11)	546
	16	1,200	17·6	2·6	1·8 (9)	573	667 (2)	562

* Interval studies not done.
† Values represent lowest level of serum urate and highest level of urine urate obtained.
‡ Number in parenthesis represents the day of therapy the maximum value was obtained.

cent., an increase of 53 per cent. over control values. In these studies, nine out of ten patients showed a positive increase. Case 9, who developed fluid retention, had a mean *decrease* of 133 mg. per 24 hrs.

The mean change in the 24-hr urinary urate excretion in the non-gouty subjects was less marked and not significant when analysed by the same statistical method. The mean increase for the nine studies in the non-gouty subjects during the period of phenylbutazone administration was 69 mg., an increase of 12 per cent. over the mean control value. The positive change over control values expressed in percentage variation was 3 to 60 in seven out of nine instances. Cases 11 and 16, having a mean excretion less than the control, developed objective manifestations of fluid retention. Case 10 had a mean excretion increase of 3 per cent. while receiving 400 mg. phenylbutazone daily with a resulting serum phenylbutazone level of 9 mg. per cent.

The response of Case 2 (a patient with gout) to a daily dose of 800 mg. phenylbutazone is illustrated in Fig. 1. The serum uric acid values were between 7·2 and 8·0 mg. per cent. during the three control days. There was a progressive and stepwise fall of the serum urate, beginning after the first day of therapy and reaching the maximum decrease after the sixth day. The urinary excretion of uric acid increased in a corresponding stepwise fashion and reached a maximum on the sixth day of study. It will be noted that in this particular study the phenylbutazone blood level increased gradually during the first 6 days of treatment and then levelled off at approximately 15 mg. per cent. The maximum effect upon the serum level corresponds closely to the maximum blood level of the drug. The average total fall in serum urate to 4·6 mg. per cent. was reached by the eighth day. The response in this case is typical of the changes observed in both the gouty and non-gouty patients.

Fig. 2 shows a similar study in a non-gouty arthritic (Case 10) receiving 800 mg. phenylbutazone daily. Although the magnitude of the changes is not as great as in the patients with gout, the pattern is the same. The serum phenylbutazone level reached a plateau on the fifth day, at which time the serum uric acid level reached the lowest level and remained relatively constant for the duration of therapy. Urinary uric acid excretion reached its peak on the fourth day of therapy.

Urate Clearance. The effect of oral phenylbutazone on the renal clearance of urate was studied in three gouty and five non-gouty subjects (Table II, overleaf).

Simultaneous endogenous creatinine and urate clearances were determined before treatment and repeated after 8 days of therapy. Preliminary studies demonstrated that further significant change in the serum or urinary uric acid seldom occurred after 8 days of oral administration of the drug. The gouty patients had a mean control urate clearance (*Cur*) of 4·8 ml./min. which under therapy increased to 13·3 ml./min. (increase of 177·9 per cent.). The

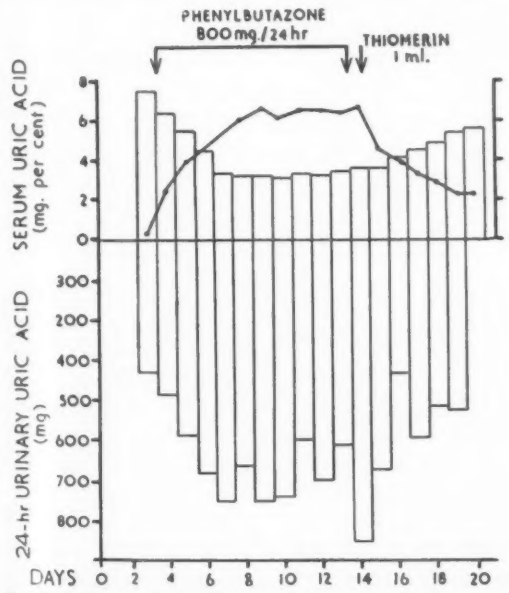


Fig. 1.—Effect of 800 mg. oral phenylbutazone daily on serum and urinary uric acid levels in a subject with gout (Case 2).

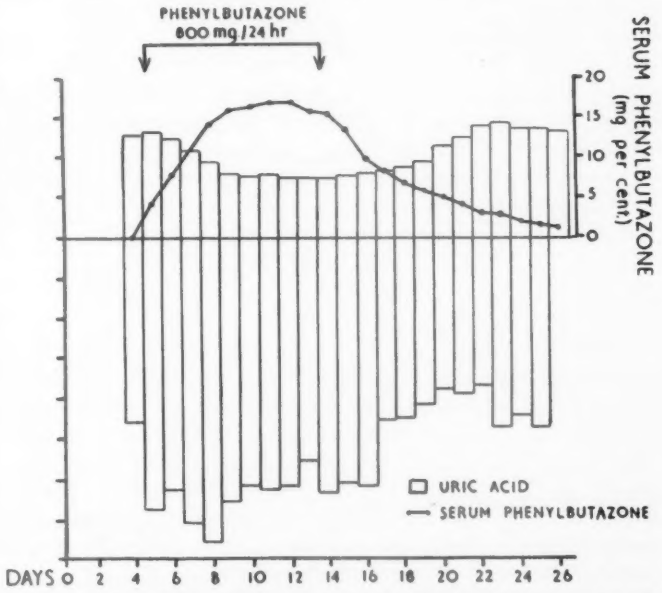


Fig. 2.—Effect of 800 mg. oral phenylbutazone daily on serum and urinary uric acid levels in a non-gouty subject (Case 10).

TABLE II

EFFECT OF EIGHT DAYS' ADMINISTRATION OF PHENYLBUTAZONE ON SERUM URATE AND RENAL CLEARANCE OF URATE

Diagnosis	Case No.	20-min. Period	Control				Phenylbutazone (mg./24 hr)	After Therapy				
			Serum Urate (mg. %)	Ccr (ml./min.)	Cur (ml./min.)	Cur / Ccr		Serum Phenylbutazone (mg. %)	Serum Urate (mg. %)	Ccr (ml./min.)	Cur (ml./min.)	Cur / Ccr
Non-Gouty	14	1	7·0	120·0	7·8	0·062	600	14·4	3·6	123·3	21·8	0·183
		2	7·2	118·9	7·1				3·4	120·1	22·5	
		3	7·2	117·9	7·3				3·5	118·2	21·7	
	13	1	5·3	105·5	9·2	0·083	600	7·5	4·7	92·4	10·2	0·108
		2	5·3	98·8	7·8				4·8	92·2	9·3	
		3	5·2	97·6	8·0				4·8	95·4	10·8	
	10	1	5·0	107·1	8·9	0·081	400	7·9	4·7	91·7	11·3	0·147
		2	5·1	108·5	8·5				4·6	96·3	15·7	
		3							4·7	93·7	14·5	
		1					600	10·2	4·7	111·4	11·4	0·111
		2							4·3	113·2	13·6	
		3							4·5	107·6	11·8	
		1					800	12·8	4·1	105·8	20·6	0·186
		2							4·1	111·6	18·9	
		3							4·1	92·1	18·1	
	12	1	7·0	90·8	4·7	0·052	800	15·5	4·7	94·6	13·7	0·152
		2	6·8	90·0	4·9				4·6	100·2	14·5	
		3	6·8	91·0	4·6				4·6	95·3	15·8	
	15	1	6·4	89·5	6·9	0·079	800	10·8	4·5	85·2	13·8	0·196
		2	6·0	100·0	8·0				3·9	87·9	17·8	
		3	6·5	100·7	7·9				3·9	82·3	18·6	
Gouty	1	1	10·3	77·2	2·7	0·033	400	12·0	7·2	63	6·8	0·114
		2	10·3	70·7	2·3				7·1	58	7·2	
		3	10·5	84·4	2·7				7·2	56	6·1	
		1					600	16·0	6·0	64·9	12·4	0·197
		2							6·0	62·7	12·9	
		3							6·0	55·0	10·8	
	17	1	7·8	99·2	8·6	0·082	400	8·9	5·0	111·1	12·6	0·109
		2	8·0	95·1	7·9				5·0	112·1	12·7	
		3	8·3	96·1	7·5				5·0	118·7	12·3	
	2	1	7·1	83·8	3·8	0·049	600	14·5	2·8	80·7	24·7	0·272
		2	7·0	82·0	4·2				2·9	87·4	22·6	
		3	7·0	77·4	4·0				2·8	75·4	19·0	

non-gouty patients had a mean control urate clearance of 7·2 ml./min. which increased under therapy to 15·5 ml./min. (an increase of 115·2 per cent.).

The creatinine clearance under therapy decreased in both groups; falling from 85·1 to 76·7 ml./min. in the gouty subjects and from 102·5 to 100·5 ml./min. in the non-gouty. All subjects, both gouty and non-gouty, had an increase in the Clearance Urate : Clearance Creatinine ratio (*Cur* : *Ccr*). In gouty subjects the mean *Cur* : *Ccr* rose from 0·049 to 0·173 (increase of 257·1 per cent.). In the non-gouty subjects the ratio rose from 0·071 to 0·156 (increase of 115·0 per cent.). In the gouty subjects, the mean percentile change ranged from 33 to 497·7; in the non-gouty from 30·1 to 198·0.

The subjects with the lower serum phenylbutazone levels demonstrated less change in the *Cur* : *Ccr* ratios. For example, the increase in *Cur* : *Ccr* for the three subjects with phenylbutazone levels below 10 mg. per cent. was 48·21 per cent. above the mean control; patients with levels above 10 mg. per cent. showed an increase of 346·24 per cent. The mean change in the serum urate with drug levels above 10 mg. per cent. was 38·5 per cent., and below 10 mg. per cent. the change was 20·9 per cent.

Phenylbutazone Serum Determinations.—Serum phenylbutazone levels were obtained after 8 days of oral therapy in 73 instances. Previous studies (Figs 1 and 2) in this laboratory and elsewhere (Brock, 1953) have shown that by the eighth day on any given dosage, the serum phenylbutazone has reached a constant level which is unaltered by further administration of the same dosage of the drug. It is apparent from Fig. 3 that increasing dosages up to 600 mg./24 hrs result in a steep rise in the corresponding serum levels. Increasing daily dosages above 600 mg. produced a less marked rise in the

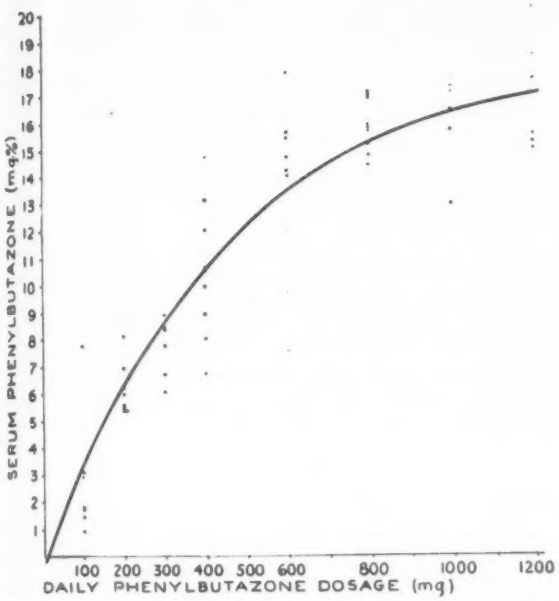


Fig. 3.—Serum phenylbutazone levels after 8 days' oral administration of phenylbutazone.

serum phenylbutazone level. For example, it will be noted that the difference in the average serum phenylbutazone level of patients receiving 200 mg. and 600 mg. orally per day was 7·2 mg. per cent., while the difference in average serum levels of patients receiving 600 and 1,000 mg. per day of the drug was only 2·5 mg. per cent.

All but three of thirteen patients receiving 600 mg. and all the patients receiving 800 mg. or above daily had serum levels above 10 mg. per cent. Figs 1 and 2 demonstrate the rate of increase of serum phenylbutazone when a patient is started on a daily oral intake of 800 mg. The pattern of response is similar for all dosages, but the rate of increase varies for different dosages. All of five patients receiving dosages of 800 mg. daily or above had serum levels in excess of 10 mg. per cent. by the third day. On the contrary, in four patients receiving 600 mg. daily, a 10 mg. per cent. level was not reached until the 6th day. The serum response to any given daily oral intake of phenylbutazone varied considerably. The range of variation for all doses averaged 6 mg. per cent. After cessation of therapy there was a gradual decline in the serum level over a 7- to 14-day period.

Discussion

The observations reported in this paper would add phenylbutazone to the list of substances which alter the urate tubular transport mechanism. The increased excretion of urate is contrary to the reports of others (Kuzell and others, 1952, 1954; Kidd, Boyce, and Freyberg, 1953; Johnson and others, 1954; Mason, 1954) and in accord with the work of Yü, Sirota, and Gutman (1953). The studies herein presented have demonstrated in both gouty and non-gouty arthritics a consistent fall in the serum uric acid, an increased clearance of uric acid, and in the gouty subjects a significant increase in 24-hr urate excretion. The mean 24-hr urinary urate excretion for the non-gouty subjects, while not statistically significant, did rise in seven out of nine instances. In both groups, all subjects except Case 9 had single 24-hr urinary excretions of urate which exceeded the control value, and preceded (in sixteen out of nineteen instances) the maximum fall in the serum urate.

It is evident from this data that the alteration in renal function is one of the major mechanisms responsible for the decrease in the serum urate in gouty subjects. The fact that in one gouty and two non-gouty subjects the serum urate level fell while the mean 24-hr urate excretion did not rise, indicates that other mechanisms are at work in decreasing the serum urate level during phenylbutazone therapy. Indeed, Delfel and Griffin (1953), studying the effect of phenylbutazone on rat liver homogenate, reported that the drug apparently decreased the catabolism of nucleic acid. Further, it has been shown that phenylbutazone increases the blood volume (Wilkinson and Brown, 1953; Brodie and others, 1954), thus causing a decrease due to dilution of the serum urate. It is to be noted that all three of the subjects in whom the serum urate fell without a corresponding increase in the urinary urate developed oedema and other manifestations of fluid retention. Fluid retention would appear to explain some of reported observations of the effect of phenylbutazone on serum urate. Johnson and others (1954) studied two patients who were given 1,000 mg. of the drug daily, and manifested considerable suppression of all the urinary constituents studied: 24-hr volume, creatinine, urate, sodium, and 17-hydroxy-corticoids. The diversity of substances affected suggests that a general mechanism, such as fluid retention, is responsible for the serum urate change. Mason (1954) noted that, where water retention did not supervene, a marked uricosuric action was effected by the drug. He concluded that phenylbutazone had a slight uricosuric effect and also a salt-and-water retaining effect. Kuzell and others (1952, 1954) put forth no urate excretion data to substantiate their claim that the serum urate falls without a corresponding increase in the urine urate. Kidd, Boyce, and Freyberg (1952,

1953) present little data to support their conclusion that urate excretion is not affected by phenylbutazone. The determinations of urate excretion were not consecutive, and would seem insufficient for this type of study.

Phenylbutazone caused an increased clearance of serum urate in both gouty and non-gouty subjects. The data presented here supports the conclusion of Yü, Sirota, and Gutman (1953) that serum phenylbutazone levels above 10 mg. per cent. are necessary to produce a significant increase in the clearance of urate. They noted in short-term infusion experiments that serum phenylbutazone levels below 10 mg. per cent. did not significantly increase urate clearance. The subjects in this study with serum phenylbutazone levels below 10 mg. per cent. had an increase in the *Cur* : *Ccr* ratio of 48 per cent., compared with 345 per cent. in those with drug levels above 10 mg. per cent.

While serum levels of phenylbutazone above 10 mg. per cent. are necessary to obtain a marked increase in the clearance of urate, it would appear that this drug may be useful as a uricosuric agent. A daily intake of 600 mg. or more is necessary to bring about a serum phenylbutazone level of 10 mg. per cent. or above. Since in our experience the incidence of toxicity of patients receiving oral phenylbutazone on dosages above 600 mg. per cent. is greatly increased, this limits the clinical use of this drug as a long-term uricosuric agent.

The majority of acute attacks of gout can be aborted within 8 to 12 hrs on dosages of either 100 or 200 mg. every 4 hrs. It is apparent that this particular therapeutic effect is not dependent upon any change in renal function, since the serum phenylbutazone response to orally administered doses of this magnitude seldom results in a serum level high enough to cause a uricosuric effect.

Summary

(1) Phenylbutazone is an effective therapeutic agent in acute attacks of gout.

(2) Orally administered phenylbutazone is a uricosuric agent.

(3) The fall in the serum uric acid induced by phenylbutazone in the gouty subject corresponds to the increased urinary uric acid excretion.

(4) Three patients in this study demonstrated a fall in serum urate with a decreased mean 24-hr urate excretion. These patients manifested marked fluid retention, and this appears to be a factor in the lowering of serum urate concentration.

(5) The uricosuric effect can be clearly demonstrated at serum phenylbutazone levels above 10 mg. per cent.

(6) Dosages above 600 mg./24 hrs are necessary to obtain a consistent uricosuric effect.

(7) Acute attacks of gout are aborted at serum levels insufficient to cause a uricosuric effect.

(8) On a regular daily oral dose, serum phenylbutazone levels reach a plateau between the sixth and eighth day of therapy and remain relatively constant thereafter.

The phenylbutazone used in these studies was supplied by the Geigy Pharmaceuticals Inc., of New York, through the courtesy of Dr. Albert Hemming to whom we express our appreciation. The authors gratefully acknowledge the co-operation given this project by the nursing and dietetic departments of the Veterans Administration Hospital, Denver, Colorado.

REFERENCES

Bonsnes, R. W., and Taussky, H. H. (1945). *J. biol. Chem.*, 158, 581.
Brock, E. (1953). Annual Report, West London Hospital, Department of Rheumatic Diseases. *Annals of the Rheumatic Diseases*, 13, 252.
Brodie, B. B., Lowman, E. W., Burns, J. J., Lee, P. R., Chenkin, T., Goldman, A., Weiner, M., and Steele, J. M. (1954). *Amer. J. Med.*, 16, 181.
Burns, J. J., Rose, R. K., Chenkin, T., Goldman, A., Schulert, A., and Brodie, B. B. (1953). *J. Pharmacol.*, 109, 346.
Delfel, N. E., and Griffin, A. C. (1953). *Stanford med. Bull.*, 11, 65.
Engleman, E. P., Krupp, M. A., Forsham, P., Griffin, A. C., Johnson, H., Green, T., and Goldfien, A. (1953). *Amer. J. Med.*, 15, 414.
Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G. (1948). *J. clin. Endocr.*, 8, 15.
Huffman, E. R., Smyth, C. J., Wilson, G. M., Hill, R. (1953). *Proc. cent. Soc. clin. Res.*, 26, 49. (Abstr. *J. Lab. clin. Med.*, 42, 818.)
Johnson, H. P., Engleman, E. P., Forsham, P. H., Krupp, M. A., Green, T. W., and Goldfien, A. (1954). *New Engl. J. Med.*, 250, 665.
Kidd, E. G., Boyce, K. C., and Freyberg, R. H. (1952). *Annals of the Rheumatic Diseases*, 11, 297.
——, ——, —— (1953). *Ibid.*, 12, 20.
Kuzell, W. C., Schaffarzick, R. W., Brown, B., and Mankle, E. A. (1952). *J. Amer. med. Ass.*, 149, 729.
——, ——, Naugler, W. E., Gaudin, G. P., Mankle, E. A., and Brown, B. (1954). *Amer. J. Med.*, 16, 212.
Mason, R. M. (1954). *Brit. med. J.*, 1, 788.
Smyth, C. J. (1953). *J. Amer. med. Ass.*, 152, 1106.
Steinbrocker, O., Berkowitz, S., Ehrlich, M., Elkind, M., and Carp, S. (1952). *Ibid.*, 150, 1087.
Stephens, C. A. L., Jr., Yeoman, E. E., Holbrook, W. P., Hill, D. F., and Goodin, W. L. (1952). *Ibid.*, 150, 1084.
Wilkinson, E. L., and Brown, H. (1953). *Amer. J. med. Sci.*, 225, 153.
Yü, T. F., Sirota, J. H., and Gutman, A. B. (1953). *J. clin. Invest.*, 32, 1121.

Effet métabolique de la phénylbutazone dans l'arthrite goutteuse et non-goutteuse

RÉSUMÉ

(1) La phénylbutazone est un agent thérapeutique efficace contre l'attaque aiguë de goutte.

(2) Administrée par voie buccale, la phénylbutazone est un agent uricosurique.

(3) La chute de l'acide urique dans le sérum, produite par la phénylbutazone chez les goutteux, correspond à son excrétion urinaire augmentée.

(4) Trois malades dans cette série manifestèrent une chute sanguine des urates accompagnée de leur baisse excrétoire moyenne par 24 heures. Chez tous les malades on observa une retention aqueuse marquée, ce qui semble jouer un rôle dans la baisse de la concentration sanguine des urates.

(5) L'effet uricosurique est nettement demontrable aux taux sériques de la phénylbutazone au-dessus de 10 mg. pour cent.

(6) Des doses supérieures à 600 mg. par 24 heures sont nécessaires pour obtenir un effet uricosurique décisif.

(7) Des attaques aigus de goutte sont avortés à des taux sériques trop bas pour causer un effet uricosurique.

(8) La phénylbutazone, prise régulièrement par voie buccale, atteint entre le sixième et le huitième jour un taux sérique qui demeure à peu près constant.

Efecto metabólico de la fenilbutazona en la artritis gotosa y otra

SUMARIO

(1) La fenilbutazona es un agente terapéutico eficaz en el ataque agudo de gota.

(2) Por vía oral, la fenilbutazona es un agente uricosúrico.

(3) La baja del ácido úrico en el suero, producida por la fenilbutazona en los gotosos, corresponde a su excreción urinaria aumentada.

(4) En tres enfermos de este grupo hubo una baja sanguínea de uratos acompañada de la reducción de la excreción media por 24 horas. Todos los enfermos acusaron una retención hídrica marcada, lo que parece jugar un papel en la baja de la concentración sérica de uratos.

(5) El efecto uricosúrico es claramente demostrable con concentraciones sanguíneas de fenilbutazona de más de 10 mg. por ciento.

(6) Para obtener un efecto uricosúrico decisivo se necesitan doses superiores a 600 mg. por 24 horas.

(7) Ataques agudos de gota se ven abortados con concentraciones sanguíneas insuficientes para causar un efecto uricosúrico.

(8) Con tomas diarias por vía oral, la fenilbutazona alcanza entre el sexto y el octavo día un nivel sanguíneo determinado que se mantiene relativamente fijo.

RHEUMATIC FEVER AS A COLLAGEN DISEASE*

BY

D. A. LONG

From the National Institute for Medical Research, London

(RECEIVED FOR PUBLICATION SEPTEMBER 23, 1954)

Rheumatic fever is typical of the collagen diseases in that lesions of mesenchyme, heart, blood vessels, joints, and serous membranes are frequently associated with hyperglobulinaemia, lymphadenopathy, and splenomegaly. Not only is the disease typical but it occurs more frequently and, being a prepubertal disease, is less complex than most of the diseases of the group. There are, therefore, several clues to its aetiology. These clues provide evidence by analogy as to the nature of collagen diseases in general.

Haemolytic Streptococci.—Group A haemolytic streptococci are the most important factor in the pathogenesis of rheumatic fever. There is no simple bacteria-host relationship that can be defined in terms of Koch's postulates. It is the host, not the streptococcus, that decides the issue, for few patients with haemolytic streptococcal infection develop the disease. The syndrome occurs when recurrent attacks of haemolytic streptococcal tonsillitis have led to marked localization of the infection, a high level of antibodies, and frequently minimal constitutional disturbance until the development of rheumatic fever. The disease is part of what Rantz and others (1946) have termed "the post-streptococcal state". This state is always associated with hypersensitivity (of the tuberculin type) to streptococcal allergens; in the guinea-pig, at least, cells damaged by a specific streptococcal toxin are more susceptible to bacterial allergens than cells not so damaged, and this may in part explain the particular role of the streptococcus (Grey and Long, 1954). But the full rheumatic syndrome does not necessarily occur in all patients exhibiting sensitivity to streptococcal allergens.

Nutritional Factors

Essential Aminoacids.—It has been suggested that, of the many agents that influence susceptibility (Waksman, 1949), nutritional and hormonal factors are the most important (Long, 1954), and that, in particular, a deficiency in essential sulphur containing aminoacids is in part responsible for increased susceptibility to the disease. In support of this hypothesis is the fact that essential aminoacids cannot be stored and therefore a deficiency is readily induced. Rheumatic fever is less common in the protein-eating farming states than in the cotton and tobacco states of America (Peete, 1944). Egg consumption is lower in children who develop rheumatic fever than in those who do not (Wallis, 1954). Powdered egg yolk prevented recurrence of rheumatic fever in underprivileged children in spite of recurrent attacks of haemolytic streptococcal infection (Coburn and Moore, 1943). It is noteworthy that hyperglobulinaemia and multiple small areas of cardiac necrosis have been described in conditions attributed to a deficiency of animal protein (Davies, 1952), and that of all sources of protein, egg protein has the highest biological value (Block and Mitchell, 1946). Gamma globulin can be synthesized extrahepatically even when a deficiency of essential aminoacids has impaired hepatic synthesis of albumin. Whipple and others (1942) showed that although the body cannot store protein, there are large reserves in tissues which can be withdrawn without impairing vital function. Plasma proteins are readily replaced from tissues; conversely, plasma proteins injected intravenously can supply all the protein requirements of the body, suggesting that plasma protein can be readily incorporated into tissues. Neuberger and his colleagues (Harkness and others, 1954) have shown in the rat that protein electrophoretically indistinguishable from plasma protein is present, probably extra-cellularly, in large amounts in close association with the collagenous protein of connective tissue. It has been suggested that in the collagen diseases in general, and rheumatic fever in particular, connective tissue provides protein and globulin for the general metabolic pool (Long, 1954), this loss being associated with characteristic degenerative changes in mesenchyme.

* Read at the Third International Congress of Internal Medicine in Stockholm on September 16, 1954.

Humphrey and McFarlane (1954) have recently shown that gamma globulin provides aminoacids for incorporation into liver cells. It is possible that under conditions of protein deficiency hyperglobulinaemia represents a compensatory phenomenon to increase the supply of aminoacids to the liver.

Ascorbic Acid.—Large amounts of ascorbic acid are needed to saturate and to maintain saturation in patients with rheumatic fever, with rheumatoid arthritis, and with active tuberculosis. It is possible that such patients oxidize ascorbic acid more readily than other patients and that this hypothesis might, through the intermediary glutathione, be linked with a deficiency of sulphur-containing aminoacids (Long, 1954).

Hormonal Factors

Of the various hormones, insulin and cortisone provide the most important clues.

Insulin.—Rheumatic fever seldom occurs in diabetics (Barach, 1926; Joslin, 1937); the development of diabetes in rheumatic patients reduces the incidence of heart damage (Joslin, 1937). Conversely, patients with rheumatic fever show "functional hyperinsulinism" (Steincrohn, 1938; Abrahamson, 1944). The symptoms of rheumatoid arthritis are relieved during the compensatory phase that succeeds insulin hypoglycaemia (Kersley and others, 1951). Two further facts are noteworthy: insulin and glutathione are closely related (Houssay, 1950), and the islets of Langerhans alone among the endocrine glands obtain their nerve supply from the parasympathetic.

Cortisone.—This relieves the symptoms of rheumatic fever and of many of the collagen diseases. The nerve supply of the adrenal cortex is from the sympathetic. Cortisone antagonizes many of the actions of insulin. It transfers aminoacids from carcase to liver, a phenomenon frequently associated with a reversion of hyperglobulinaemia to normal levels. It is possible that by this means cortisone makes good a deficiency in the liver of essential aminoacids and so removes the stimulus that induces hyperglobulinaemia. Again, the biological activity of cortisone is closely linked with the metabolism of glutathione (Long, 1954).

Conclusions

Rheumatic fever occurs in patients with marked hypersensitivity (of the tuberculin type) to streptococcal allergens. Eggs, and probably biologically valuable protein, decrease susceptibility to the disease. Hyperinsulinism increases, and hypoinsulinism decreases, susceptibility. Cortisone decreases susceptibility. Ascorbic acid requirements are increased. The common factor relating hypersensitivity to these nutritional and hormonal agents is the metabolism of sulphur-containing aminoacids and of glutathione.

These ideas have been criticized for being too complex. "The best hypotheses are the simplest. All current theories about the aetiology of rheumatic fever are complicated, and none more so than that recently suggested by Long" (Annotation, 1954). Of course, of any two hypotheses, either of which will

TABLE

ANALOGY BETWEEN RHEUMATIC FEVER IN MAN AND THE B.C.G.-INFECTED GUINEA-PIG*

Lines of Inquiry		Man (Rheumatic fever)	Guinea-pig (B.C.G.-infected)
Bacterial Allergy (Tuberculin type)		+	+
Ascorbic-acid Synthesis		−	−
Cortisone	1. General resistance	+	+
	2. Particular resistance (Gamma-globulin synthesis	+	+
	2. Particular resistance (Antitoxin synthesis	+	+
	3. Anti-allergic action	+	+
	4. Anti-inflammatory action	−?	−
	5. Specificity of molecule	+	+
Insulin	Diabetogenic agents	↓	↓
	Antidiabetogenic agents	↑	↑
Thyroid	Hyperthyroidism	↑	↑
	Hypothyroidism	↓	↓
–SH (Reduced glutathione)		?	↑
Anti –SH		?	↓

↓ Decrease susceptibility ↑ Increase susceptibility * For detailed argument see Long (1954).

explain all the facts, the simpler is to be preferred. But what simple hypothesis will unite bacterial, allergic, nutritional, and hormonal hypotheses, or explain the analogy between the tuberculin sensitive guinea-pig and rheumatic fever? (Table). By considering a single facet of the problem and ignoring the rest, a simple hypothesis can be produced, but this is at the cost of seeking simplicity where none exists.

Rheumatic fever, though complex, is the collagen disease of which we know most; I have selected clues which can be followed and which may lead to a fuller understanding of the group as a whole.

REFERENCES

Abrahamson, E. M. (1944). *J. clin. Endocr.*, **4**, 71.
Annotation (1954). *Brit. med. J.*, **1**, 924.
Barach, J. H. (1926). *Amer. Heart J.*, **2**, 196.
Block, R. J., and Mitchell, H. H. (1946). *Nutrition Abstr. Rev.*, **16**, 249.
Coburn, A. F., and Moore, L. V. (1943). *Amer. J. Dis. Child.*, **65**, 744.
Davies, J. N. A. (1952). *Ann. Rev. Med.*, **3**, 99.
Grey, R. C., and Long, D. A. (1954). *Brit. J. exp. Path.*, **35**, 85.
Harkness, R. D., Marko, A. M., Muir, Helen M., and Neuberger, A. (1954). *Biochem. J.*, **56**, 558.
Houssay, B. A. (1950). *Amer. J. med. Sci.*, **219**, 353.
Humphrey, J. H., and McFarlane, A. S. (1954). *Biochem. J.*, **57**, 195.
Joslin, E. P. (1937). "The Treatment of Diabetes Mellitus", 6th ed. Lea and Febiger, Philadelphia.
Kersley, G. D., Mandel, L., Jeffrey, M. R., Bene, E., and Taylor, K. B. (1951). *Brit. med. J.*, **2**, 574.
Long, D. A. (1954). *Lancet*, **1**, 529.
Steincrohn, P. J. (1938). *J. Amer. med. Ass.*, **111**, 1837.
Peete, D. C. (1944). *Ann. intern. Med.*, **21**, 44.
Rantz, L. A., Spink, W. W., and Boisvert, P. J. (1946). *Arch. intern. Med.*, **77**, 66.
Waksman, B. H. (1949). *Medicine, Baltimore*, **28**, 143.
Wallis, A. D. (1954). *Amer. J. med. Sci.*, **227**, 167.
Whipple, G. H. (1942). *Proc. Inst. Med. Chicago*, **14**, 2.

Rhumatisme articulaire aigu comme maladie collagène

RÉSUMÉ

Le rhumatisme articulaire aigu survient chez des personnes douées d'une hypersensibilité marquée (type de tuberculine) aux allergènes streptococciques. Des oeufs et probablement des protéines biologiquement utiles réduisent la susceptibilité à cette maladie. De même l'hypoinsulinisme la réduit tandis que l'hyperinsulinisme l'accentue. La cortisone réduit la susceptibilité. La demande d'acide ascorbique se trouve augmentée. Comme facteur commun entre l'hypersensibilité et les agents nutritifs et hormonaux mentionnés on trouve le métabolisme des aminoacides contenant du soufre et celui du glutathione.

Le rhumatisme articulaire aigu, bien que complexe, est une des maladies collagènes que nous connaissons mieux; j'ai indiqué les pistes à suivre pouvant mener au meilleur entendement de l'entier groupe morbide.

Reumatismo poliarticular agudo como enfermedad colagena

SUMARIO

El reumatismo poliarticular agudo ocurre en personas con hipersensibilidad marcada (tipo de tuberculina) a los alérgenos estreptocóccicos. Huevos y probablemente proteinas biológicamente útiles reducen la susceptibilidad a esta enfermedad. Asimismo el hipoinsulinismo la reduce mientras que el hiperinsulinismo la aumenta. La cortisona reduce la susceptibilidad. La demanda de ácido ascórbico se ve aumentada. Como factor común entre la hipersensibilidad y los agentes nutritivos y hormonales mencionados encuéntrase el metabolismo de los aminoácidos que contienen azufre y la glutatión.

El reumatismo poliarticular agudo, aunque complejo, es la enfermedad colagena que conocemos mejor; he indicado aquí pistas que pueden llevar a la mejor comprensión del grupo mórbido entero.

BONE MARROW IN RHEUMATOID ARTHRITIS

BY

JACQUES HOULI and H. MONTEIRO MARINHO

From the Rheumatological Department, Fifth Chair of Internal Medicine, University of Brazil

(RECEIVED FOR PUBLICATION JUNE 28, 1954)

Various results have been reported from the study of the bone marrow in patients with rheumatoid arthritis. These include "hypocellularity" (Merlo and Tortori Donati, 1945), "general granulocytic hyperplasia" (Lucchesi, Lucchesi, and da Silva, 1946), reticulo-endothelial hyperactivity (Marmont, 1948), and a slight increase of metamyelocytes and decrease in the formation of buds of megacaryocytes (Jeffrey, 1952). The last, which also occurs in thrombocytopenic idiopathic purpura, could presumably be taken as an evidence of a slight degree of hypersplenism in patients with rheumatoid arthritis (Curtis and Pollard, 1940). This hypothesis seems to be substantiated by the fact that in some cases with leukopenia in the peripheral blood, the bone marrow was hyperplastic, which suggests a possible inhibitor factor. It is interesting to note that some published reports mention good results obtained in patients with rheumatoid arthritis following splenectomy (Bach and Jacobs, 1951).

In ten non-selected cases of rheumatoid arthritis, Hayhoe and Smith (1951) found 1·8 to 6·3 per cent. (normal 2 per cent.) of plasma cells by bone marrow biopsy, and a significant and constant increase in serum globulin, but it did not seem that either plasmocytosis or hyperglobulinaemia were due to the activity of the disease, as no parallelism was observed between them. This opinion was not shared by Jasiński and Staehelin (1951), who reported normal plasma cell counts in patients with the disease.

A study of 32 children with Still's disease, in its various stages, showed general bone marrow hyperplasia, especially affecting the granulocytic cells, which, in 29 cases, made up 60 per cent. or more of the total count. A shift to the left of the granulocytes was observed with pro-myelocyte rates of 20 and 30 per cent. myelocytes of the total bone marrow cells (Schlesinger and Cathie, 1951). An increase in the immature elements was reported from other series as well as the presence of a great number of megacaryocytes.

Curtis and Pollard (1940) reported a relative decrease in immature erythroblastic cells in half of sixteen cases in which the peripheral red blood count revealed the presence of anaemia; this finding suggested the hypothesis of a disturbed formation of normoblasts as an explanation for the anaemia of rheumatoid arthritis.

The study of the bone marrow in 21 cases of rheumatoid arthritis by Marmont (1948) showed the presence of megaloblastic forms, hyperactivity of reticulum elements, and transition cells from primitive reticular cells and basophil erythroblasts. A decrease of haemocytoblasts, plasmo-cellular hyperplasia (Marmont, 1948), and eosinophilia was observed to occur simultaneously with the change found in the peripheral blood count (Volpicelli, 1951).

Present Investigations

We have recently had the opportunity of studying the bone marrow in twenty patients with rheumatoid arthritis.

The material analysed was obtained by biopsy-punction, by aspiration of sternal bone marrow, and the preparations were coloured by the panoptic method of Pappenheim. In ten cases (1 to 10) 600 cells were counted, in three cases (11, 12, and 13) 400 cells, in two (14 and 15) 300 cells, and in the rest (16 to 20) only 200.

The twenty patients were classified according to the stage of the disease:*

I. Initial, two cases;
II. Moderately advanced, eleven cases;
III. Advanced, seven cases;
IV. Terminal, none.

* Steinbrocker and others (1949).

TAB
RESULTS OF BONE

Case Nos.	1	2	3	4	5	6	7	8	9
Stage of Disease	II	III	II	II	II	III	III	II	II
Haemocytoblasts	0·3	0·3	0·2	0·5	0·3	—	0·2	—	0·2
Myeloblasts	2·8	0·3	1·2	3·0	1·3	3·0	3·0	1·0	2·6
Pro-myelocyte neutrophils	2·6	0·7	1·8	3·5	2·9	2·2	2·2	0·3	1·8
Myelocyte neutrophils	8·0	10·0	8·6	12·0	10·0	9·0	4·6	11·6	26·6
Metamyelocytes	12·3	6·6	21·2	14·5	11·6	7·0	9·6	10·3	16·8
Band-form neutrophils	16·5	15·0	15·0	9·5	16·3	15·6	0·8	14·0	11·2
Segmented forms	22·8	28·6	21·0	34·5	18·6	36·3	23·0	36·3	11·0
Pro-myelocyte eosinophils	0·5	1·7	1·0	0·5	—	1·3	1·8	—	0·6
Myelocyte eosinophils	—	—	—	—	—	—	1·8	—	—
Metamyelocyte eosinophils	—	—	—	—	—	—	1·8	—	—
Eosinophils	2·0	6·6	4·0	4·0	1·0	5·6	8·0	3·3	1·0
Myelocyte basophils	—	—	—	—	—	—	—	—	—
Basophils	0·5	—	—	—	—	0·3	0·2	0·6	0·2
Lymphocytes	7·3	4·3	6·2	4·5	6	10·3	3·4	8·3	1·8
Monocytes	0·3	0·3	—	0·5	—	0·3	—	1·0	—
Histiocytes	—	—	—	—	—	—	—	—	—
Plasmocytes	3·3	1·7	0·6	0·5	0·6	1·0	4·0	0·3	—
Pro-erythroblasts	0·8	0·3	1·8	—	0·3	—	—	0·3	0·2
Erythroblast basophils	1·6	1·7	4·0	2·0	2·3	4·3	5·4	0·6	4·2
Erythroblast polychromatophils	16·6	19·3	12·8	6·0	19·3	6·6	25·6	10·6	21·6
Erythroblast orthochromatics	2·0	1·3	1·0	0·5	6·6	2·0	1·8	0·6	0·2
Megacaryocytes	S	S	S	N	S	S	S	S	S
Leuco-erythroblastic ratio	3·5 : 1	3 : 1	4 : 1	9 : 1	2·3 : 1	5·8 : 1	3 : 1	6 : 1	2·8 : 1

N = normal.

Results

The results are presented in Table I.

Eosinophilia.—This was observed in seven cases (2, 6, 7, 13, 15, 16, 19; 35 per cent.). Comparing the bone marrow eosinophilia with that observed in peripheral blood counts (Table II), we observed similar counts in four cases. In another case the peripheral blood eosinophil count was normal. In the remaining two such a comparison was not possible.

TABLE II
COMPARISON OF BONE MARROW AND PERIPHERAL BLOOD EOSINOPHILIA

Case Nos.	Relative Bone Marrow Eosinophilia	Relative Peripheral Eosinophilia
2	6·6	9
6	5·6	6
7	14·7	6
13	17	—
15	13·5	—
16	8	4
19	24	22

Plasma Cells.—The plasma cell counts were above normal in only five cases (1, 7, 11, 14, 18; 25 per cent.). The increase varied between 3 and 5·3 (Table I). The distribution of the plasmocytosis of the bone marrow, according to the stage of the disease was:

I. two cases;
II. two cases;
III. three cases;
IV. none.

We investigated the possibility of correlating bone marrow plasmocytosis with the blood protein changes determined by the flocculation tests (cephalin-cholesterol, colloidal red, Gross-Jacobson, and cadmium sulphate). We selected a group of five "control" patients with rheumatoid arthritis at the same stage, in whom the bone marrow was normal, and compared the results of the flocculation tests with the five which showed plasmocytosis. Table III shows that the flocculation tests were generally positive whether or not there was plasmocytosis. Therefore we can conclude, allowing for objections due to the small number of cases studied, that there is no apparent correlation between bone marrow plasmocytosis and blood protein alterations measured by flocculation tests.

TABLE III
COMPARISON OF FLOCCULATION TEST IN PATIENTS WITH PLASMOCYTOSIS AND CONTROLS

Flocculation Tests	Five Rheumatoid Patients with Bone-marrow Plasmocytosis					Five Rheumatoid Patients with Normal Plasmocytes in the Bone Marrow				
	1	7	11	14	18	F	G	H	J	K
Cephalin Cholesterol	4	3	3	—	3	2	3	3	2	3
Colloidal Red	3	4	3	—	4	3	3	0	3	3
Gross-Jacobson	1	0	0	—	—	2	3	0	2	1
Cadmium Sulphate	2	1	3	½	2	2	3	0	2	1
Evolutive Stage of the Disease	II	III	II	III	III	II	III	II	III	III

Leuco-Erythroblastic Ratio.—This relation was normal in ten cases, depressed in five, and raised in five.

L.E. Cells.—The type of lesion found in patients with rheumatoid arthritis as well as its generalized distribution suggest that this condition should be

LE I
MARROW BIOPSY

10	11	12	13	14	15	16	17	18	19	20	Normal Range
I	II	II	I	III	III	III	II	III	III	II	
—	—	0·205	—	0·5	1·0	—	0·3	1·0	—	N	0·1–0·3
0·6	5·0	0·705	0·5	1·0	1·0	—	—	1·0	—	N	1·2–2·5
0·6	2·5	0·705	0·5	1·0	0·5	1·0	1·0	0·6	1·0	N	2·3–5
9·6	2·5	6·000	12·0	12·0	10·0	5·0	11·5	1·0	6·0	N	11–17
11·3	8·5	15·000	14·0	10·0	14·5	13·5	20·0	29·1	9·0	N	8·5–12
24·0	12·5	15·500	16·5	16·0	12·5	17·5	16·5	16·6	19·5	N	8–18
20·0	25·0	19·205	15·5	22·0	8·0	26·5	5·0	17·3	21·5	N	22–31
0·6	2·5	—	—	—	—	—	—	—	—	—	2·4–4·7
—	—	2·500	4·0	—	3·5	1·0	0·5	—	4·0	N	1·5–2·5
—	—	0·705	—	—	1·5	1·0	—	1·6	1·0	N	1–2
1·6	3·5	11·500	13·0	4·5	8·5	6·0	4·5	—	19·0	N	0·5–4·7
—	—	0·000	—	1·0	—	—	—	—	—	N	—
0·3	1·0	0·205	0·5	1·0	0·5	0·5	—	—	—	N	0·2
4·6	5·5	1·500	0·5	—	—	1·0	—	1·3	1·5	N	2–7·2
1·0	1·5	0·500	—	—	—	0·5	—	0·3	—	N	0·5–6·6
—	—	—	—	—	1·0	0·5	—	1·6	1·0	N	0·5–3
1·0	3	1·000	1·5	4·5	1·0	1·0	—	5·3	0·5	N	0·5–2
—	2·5	—	—	0·5	1·5	—	1·0	0·3	0·5	N	0–1
0·6	1·5	0·705	—	—	2·0	—	1·3	0·3	0·6	N	2·5–4·2
3·6	9·0	9·500	8·5	13·0	14·0	8·0	29·5	3·6	3·5	N	9·2–14·2
13·3	2·5	13·250	13·0	12·5	15·0	16·0	9·5	9·6	10·5	N	8·5–11
N	S	0·205	0·5	0·5	1·0	0·5	0·5	0·6	0·5	N	0·03–0·4
3·5 : 1	5·3 : 1	3 : 1	3·6 : 1	2·6 : 1	2 : 1	3 : 1	1·5 : 1	4·6 : 1	5·3 : 1	—	2 : 1–4 : 1

S = present.

included in the group of collagen diseases; the main link between these conditions is the histo-pathological lesion, with all the restrictions inherent in such a broad concept.

In one form of collagenosis, lupus erythematosus disseminatus, a special type of cell described as the "L.E." cell (Hargraves, 1949) was initially found in the bone marrow and later in the peripheral blood (Haserick and Sundberg, 1948; Haserick, 1950; Haserick and Bortz, 1949; Morton, 1947; Sundberg and Lick, 1949). The L.E. cell is an adult neutrophil, with one phagocyte vacuole, which contains an amorphous homogeneous basophil mass, and stains purple by the method of Wright, and deep purple by the method of May-Grunwald-Giemsa. The neutrophil nucleus is compressed in the periphery of the cell and has a half-moon or bi-polar shape with two masses in the opposite extremities. The colouration by thymo-nucleic acid with Feulgen's reactive shows the nuclear origin of the inclusion. It is believed that it is formed by the phagocytosis of free nuclear material or by the autolysis of one or more neutrophil nuclei (Monteiro Marinho and others, 1952).

Some authors believe that the immunological phenomena represented by the formation of the L.E. cell is correlated to the increase of gamma globulin (Haserick, 1950) or one of its fractions, the so-called L.E. fraction. Other studies, however, have shown that the fraction in question was an immunological one, differing from gamma globulin (Haserick and Lewis, 1950).

Histo-chemical techniques suggest the possibility that L.E. cells probably originate from the depolymerization of nucleic acid (Gueft, 1950); the phagocyted nuclear material would be formed by desoxyribonucleic acid, partially depolymerized, possibly with a glycoprotein or mucoprotein substratum.

It is believed that the L.E. cell is specific for lupus (Haserick and Sundberg, 1948; Morton, 1947), notwithstanding the fact that it has been described in patients with multiple myeloma and other diseases (Berman, Axelrod, Goodman, and McClaughry, 1950). The reported analysis of the bone marrow of patients with rheumatoid arthritis, dermatomyositis, scleroderma, or active rheumatic fever showed negative results (Lee, Michael, and Vural, 1951).

Because of the increase in the gamma-globulin fraction found in our patients with rheumatoid arthritis, and the presence of L.E. cell in other conditions, and because we also observed in two of our patients the "butterfly" cutaneous face lesions so common in patients with lupus erythematosus disseminatus, we decided to investigate the presence of L.E. cells in a group of fifteen patients.

The method employed was that of Hamburger (1950)* with slight modifications:

Withdrawal of 5 ml. venous blood in oxalated recipients, centrifugation, and separation from plasma. After punction the collected bone marrow was placed in contact with plasma and stored at 37° C. The examination was done after 1, 2, and 3 hrs' incubation.

We selected representative cases of various stages of the disease: three in Stage I, three in Stage II, four in Stage III and one in Stage IV. The test was negative in all these fifteen patients, and also in another fifteen patients in various stages.

* We are indebted to Dr. Paul Wishart for his help in the use of Hamburger's technique.

Summary

The study of the bone marrow in twenty patients with rheumatoid arthritis revealed eosinophilia in seven cases, four of which presented concomitant eosinophilia in the peripheral blood. In five cases (20 per cent.) plasmocytosis was found; a comparison of bone marrow plasmocytosis with protein imbalance revealed by flocculation tests, showed no correlation between them. The leuco-erythroblastic ratio was normal in ten cases, depressed in five, and raised in five. L.E. cells were not found in fifteen patients who were investigated.

REFERENCES

Bach, F., and Jacobs, J. H. (1951). *Annals of the Rheumatic Diseases*, **10**, 320.

Berman, L. Axelrod, A. R., Goodman, H. L., and McClaughry, R. I. (1950). *Amer. J. clin. Path.*, **20**, 403.

Curtis, A. C., and Pollard, H. M. (1940). *Ann. intern. Med.*, **13**, 2265.

Gueft, B. (1950). *Arch. Derm. Syph. (Chicago)*, **61**, 892.

Hamburger, R. N. (1950). *Yale J. Biol. Med.*, **22**, 407.

Haserick, J. R. (1950). *Arch. Derm. Syph. (Chicago)*, **61**, 889.

——, and Bortz, D. W. (1949). *J. invest. Derm.*, **13**, 47.

——, and Lewis, L. A. (1950). *Blood*, **5**, 719.

——, and Sundberg, R. D. (1948). *J. invest. Derm.*, **11**, 209.

Hargraves, M. M. (1949). *Proc. Mayo Clin.*, **24**, 234.

Hayhoe, F. G. J., and Smith, D. Robertson (1951). *J. clin. Path.*, **4**, 47.

Jasiński, B., and Staehelin, A. (1951). *Schweiz. med. Wschr.*, **81**, 619.

Jeffrey, M. R. (1952). *Annals of the Rheumatic Diseases*, **11**, 162.

Lee, S. L., Michael, S. R., and Vural, I. L. (1951). *Amer. J. Med.*, **10**, 446.

Lucchesi, M., Lucchesi, O., and da Silva, M. P. (1946). *Rev. argent. Reum.*, **10**, 294.

Marmont, A. (1948). *Arch. "Maragliano" Pat. Clin.*, **3**, 1289.

Merlo, P., and Tortori-Donati, B. (1945). *Rass. Fisiopat. clin. terap.*, **17**, Suppl. 2, p. 37.

Monteiro Marinho, H., Couceiro, A., and Gomes, E. (1952). *Rev. méd.-cirúrg. Brasil*, No. 198, p. 449.

Morton, R. S. (1947). "A Study of the Blood and Bone Marrow in Cases of Lupus Erythematosus". Thesis, Mayo Foundation.

Schlesinger, S., and Cathie, I. A. B. (1951). *Annals of the Rheumatic Diseases*, **10**, 412.

Steinbrocker, O., Traeger, C., and Batterman, R. C. (1949). *J. Amer. med. Ass.*, **140**, 659.

Sundberg, R. D., and Lick, N. B. (1949). *J. invest. Derm.*, 12, 83.

Volpicelli, M. (1951). *In* T. Lucherini, "Semeiotica delle Malattie Reumatiche". Abruzzini, Rome.

Moelle osseuse dans l'arthrite rhumatismale Rapport sur vingt cas, y compris la recherche des cellules L.E.

RÉSUMÉ

L'étude de la moelle osseuse de vingt malades atteints d'arthrite rhumatismale révéla une éosinophilie dans sept cas, dont quatre présentèrent une éosinophilie concomitante dans le sang périphérique. Dans cinq cas (20 pour cent) on trouva de la plasmocytose; une comparaison de la plasmocytose de la moelle osseuse avec le déséquilibre protidique, trouvé par la réaction de floculation, ne montra aucun rapport entre ces deux phénomènes. Le rapport leuco-érythroblastique fut normal dans dix cas, diminué dans cinq et augmenté dans cinq cas. On ne trouva pas de cellules L.E. chez les quinze malades étudiés de ce point de vue.

La médula ósea en la artritis reumatoide Informe sobre veinte casos, con investigación de la presencia de las células L.E.

SUMARIO

El estudio de la médula ósea en veinte enfermos con artritis reumatoide reveló una eosinofilia en siete casos, cuatro de los cuales presentaron una eosinofilia concomitante en la sangre periférica. En cinco casos (20 por ciento) se encontró una plasmocitosis; la comparación de la plasmocitosis medular con el desequilibrio protídico, revelado por la reacción de floculación, no mostró relación alguna entre éstos. La razón leucoeritroblástica fué normal en diez casos, disminuida en cinco y aumentada en cinco. No encontráronse células L.E. en los quince enfermos investigados.

MUSCLE SPASM AS A CAUSE OF SOMATIC PAIN*

BY

DERYCK TAVERNER

Department of Medicine, University of Leeds

(RECEIVED FOR PUBLICATION JULY 19, 1954)

Pains which seem predominantly to affect the muscles are extremely common and many hypotheses regarding their genesis have been developed, but most of them have lost support in time. The concept of "fibrositis", so popular 20 years ago, is now almost universally suspect, and few would claim that any sound basis for it has been discovered.

But the destruction of a hypothesis, such as "fibrositis", does not eradicate the condition it was designed to explain. As has often been pointed out in discussion: "the pain is very real". Other theories are still current and should undergo the same critical treatment as did "fibrositis". For example, it is frequently suggested that muscle spasm is the cause of pain in a variety of disorders ranging from prolapsed intervertebral disk (Rose, 1954) to psychoneurosis (Holmes and Wolff, 1952).

It is such common knowledge that a sustained muscular contraction can be painful that it is not surprising that an involuntary muscular contraction —a muscle spasm—should be invoked as a cause of pain in disease. Indeed, this idea has led to the therapeutic use of muscle relaxants, such as *d*-tubocurarine (Schlesinger, 1946) and myanesin (Schlesinger, Drew, and Wood, 1948), but the results have not been very impressive.

It is important to examine the evidence on which the concept of muscular spasm as a common cause of pain is based. There is, of course, the clinical observation that some painful muscles are both tender and firm to the touch. Such observations may well be misleading and there have been many attempts to prove the existence of the postulated muscular spasm by instrumental methods.

Of these, electrical devices, as in electromyography, have been chiefly used, and one of the most frequently quoted contributions is that of Elliott (1944a). Elliott examined the electrical activity in muscles of fourteen patients who were later proved surgically to be suffering from prolapsed intervertebral disks. He inserted needle electrodes and in eight patients with muscular tenderness he found increased irritability of the tender muscles, *i.e.* needle movement produced more spontaneous electrical activity than in controls. In some of these tender muscles he also found a continuous discharge of one or more action potentials in "otherwise relaxed muscles". His records show, and he describes, single motor unit action potentials firing at rates of 8-12/sec. Spontaneous fluctuation of this activity was noted, *i.e.* a motor unit close to the electrode would disappear while more distant ones would continue. This spontaneous activity was shown to be localized to the tender areas by means of double channel recording, and it was found to disappear after infiltration with procaine. In discussing his findings, Elliott (1944b) refers to these electrical changes as muscular spasm, and suggests that this may cause pain in one of two ways: either because unphysiological muscular contraction, as in cramp, is painful, or because muscles contracting under ischaemic conditions become painful.

Other workers have investigated this problem in similar ways, but have usually obtained inconclusive results. For example, Holmes and Wolff (1952) found that psychoneurotic patients with backache showed generalized muscular hyperactivity during simple movements of one limb or during interviews provocative of conflict and hostility. This muscular activity did not invariably cause pain and the authors noted that similar amounts of vigorous muscular activity in exercise were normally well tolerated and painfree.

Before considering this evidence it is necessary to describe briefly the principles upon which electromyography is based (Weddell, Feinstein, and Pattle, 1944; Bauwens, 1948). The simplest muscle twitch is due to the contraction of a single motor unit. Increasing work results from firstly a faster rate of firing of the individual motor units, and secondly the recruitment of more motor units. A motor unit consists of one anterior horn cell, its motor nerve fibre and the hundred or more muscle fibres which it

* Paper read at a meeting of the Heberden Society, May, 1954.

supplies. The fibres of the individual motor unit are dispersed to some extent and do not form a compact anatomical structure. When the anterior horn cell fires, its dependent muscle fibres contract more or less simultaneously. If a needle electrode is placed close to the motor unit, the resulting electrical activity can be recorded with suitable electronic equipment. The action potential of a single motor unit has an amplitude of 1-2 millivolts and a duration of 5-10 milliseconds. All innervated contraction of skeletal muscle is accompanied by electrical activity which can be easily detected.

In a fully relaxed normal muscle there is complete electrical silence (Fig. 1). Slight voluntary contraction produces one or more motor unit action potentials firing at rates of 5-10/sec. As the activity increases, the rate of firing goes up to 40-50/sec. and more and more motor units are recruited until a maximal voluntary contraction results in an interference pattern of superimposed action potentials.

In practice certain difficulties may arise. The equipment used in electromyography is rather awe-inspiring, and few people relish the insertion of a large needle without an anaesthetic. Apprehension leads to muscular contraction, and one of the minor problems of electromyography is to produce the complete relaxation necessary to achieve the electrical silence mentioned. Patients who have suffered from severe pain, as in sciatica, for some time, find it hard to relax satisfactorily, and anyone with a tender muscle is likely to react to the intrusion of a needle by involuntary muscular contraction. It is clear, therefore, that the discovery of single motor units firing spontaneously does not prove that there has been pre-existing spontaneous muscular activity. In addition, we now know that irritation of nerve roots, *e.g.* by prolapsed intervertebral disks, may sometimes produce spontaneous action potentials (Richardson, 1951). Such activity often presents in the form of groups of repetitive action potentials with a characteristic electromyographic pattern. These bursts are often, but not necessarily, found in tender or painful muscles and they may be observed clinically as fasciculations. There can be little doubt that both the pain and the electrical activity are secondary to the nerve root irritation.

Spontaneous electrical activity is a common electromyographic finding and is seldom associated with pain. Activity very similar in appearance to that illustrated by Elliott is a characteristic feature

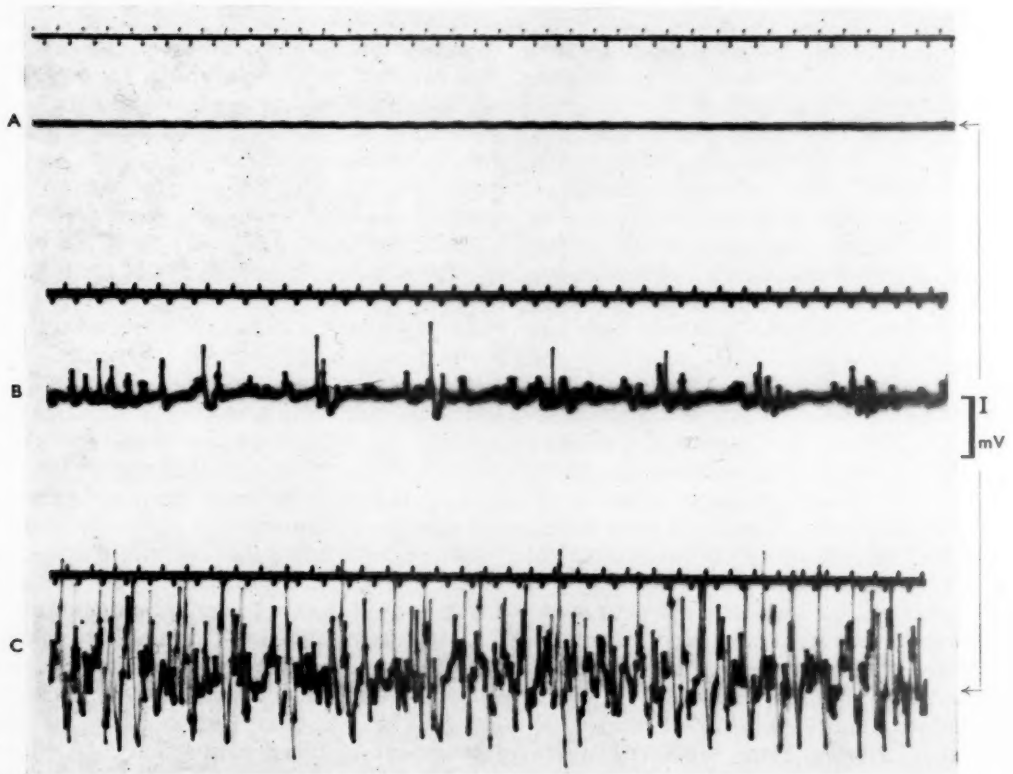


Fig. 1.—Needle electrode recordings from a normal tibialis anticus muscle. Upper beams—10 msec. time marker. Lower beams—electrical activity of muscle. A. Resting muscle. B. Slight voluntary contraction. C. Full voluntary contraction.

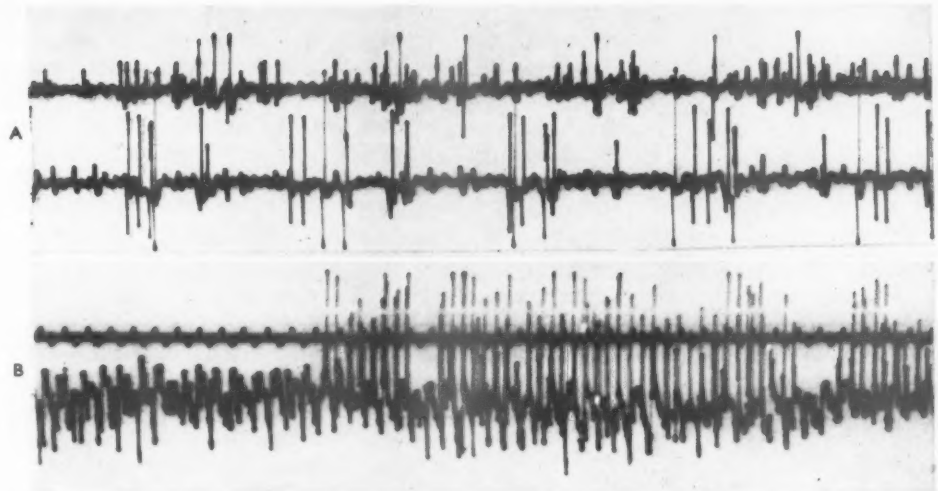


Fig. 2.—A. Simultaneous needle electrode recordings of spontaneous electrical activity from right frontalis muscle (upper beam) and right orbicularis oris muscle (lower beam) of a patient with painless facial twitching at 6 weeks' duration.
B. Needle electrode recording (lower beam) of spontaneous electrical activity in extensor communis digitorum muscle of a patient suffering from dystrophia myotonica.

of the usually painless condition, amyotrophic lateral sclerosis, and may persist for months. Fig. 2A shows a double-channel recording from the facial muscles of a patient with persistent but painless facial twitching of 6 weeks' duration. In the painless condition of dystrophia myotonica, spontaneous electrical activity of a much more striking order is constantly seen (Fig. 2B). It is true, as Elliott remarks, that muscle cramp is painful, but painful cramp is characterized by sustained electrical activity at frequencies of 300/sec. or more (Adams, Denny-Brown, and Pearson, 1953), a frequency never achieved in the most intense voluntary contraction. Fig. 3A shows the typical appearance of high frequency activity recorded from the external oblique muscle of a patient suffering from repeated painful muscle cramps. Fig. 3B shows a recording from another patient with intense muscular spasm

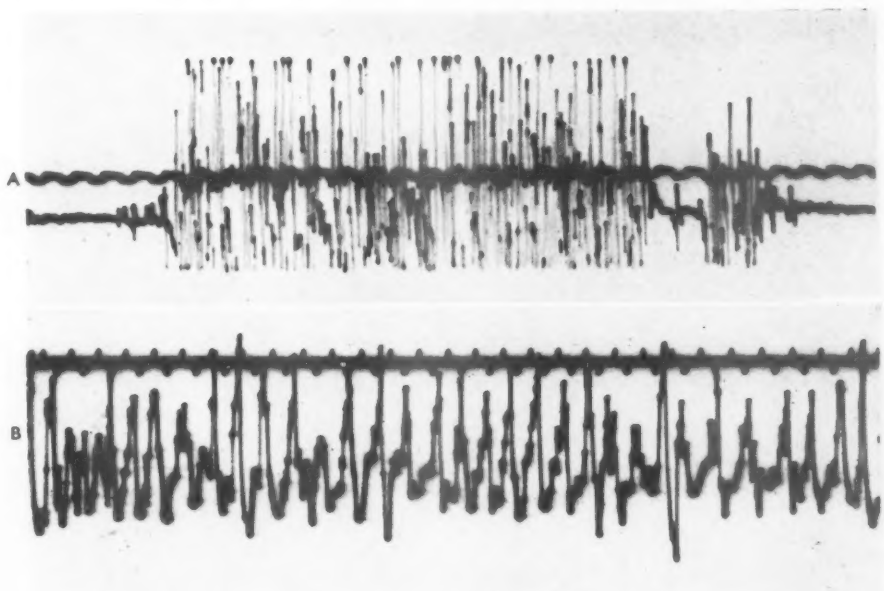


Fig. 3.—A. Needle electrode recording from external oblique muscle during a painful muscle cramp.
B. Needle electrode recording from right deltoid muscle during a painless involuntary muscle contraction or spasm.

(involuntary contraction) of his deltoid muscle. This was quite painless and it is noteworthy that the pattern is typical of a maximal voluntary contraction, but there is no sign of the high frequency activity seen in the muscle cramp.

In my own experience of electromyography in other painful conditions I have never seen spontaneous activity suggestive of cramp or, in the relaxed subject, of a degree which appeared likely to cause pain. I have, however, noted that in acute lumbago there is an abnormal degree of electrical activity in the erector spinae muscles whenever the patient makes the slightest attempt to change his position. When fully relaxed in the prone position the muscles become silent although the pain usually persists. This abnormal reactivity of the lumbar muscles is probably protective.

Yet there is no doubt that muscles do become painful after activity. The following experiment seems to exclude spasm as a cause of such muscle pain, but does raise other possibilities. The subject was a young lady who can induce typical "fibrositic" pain in the middle third of the upper border of the right trapezius muscle by knitting for about an hour. The pain leads to nausea, forces her to stop work, and is associated with marked, localized tenderness. The pain disappears in a few hours or can be immediately abolished by the injection of 1 per cent. procaine. This is a common site for such pain and it may occur, for example, after motoring.

The subject had noticed that her pain did not develop if she knitted with her right elbow supported, thus slightly reducing the activity in the right trapezius muscle, or when knitting with the right arm slightly abducted, which increases the trapezius activity. Fig. 4 shows records from two needles inserted into similar areas of the two trapezii while knitting normally (Fig. 4A), which caused pain, and while knitting with the arm abducted (Fig. 4B), which did not.

Fig. 5 shows the electrical silence in the two muscles at rest, (A) before knitting, and (B) after knitting when the pain was severe.

It is evident that there is no sign of muscular spasm under the conditions of this experiment. It is also of interest that increasing the activity of the right trapezius muscle actually prevented the onset of pain. When the subject is knitting normally, the electrical activity in the two trapezii is the same, yet pain only occurs on the right side. This girl has a slightly "dropped" right shoulder, and this is corrected by supporting the right elbow, which also prevents the development of the pain. It seems possible that the initial length of the contracting muscle may be a factor, but further study is needed.

There is little reliable evidence in support of the

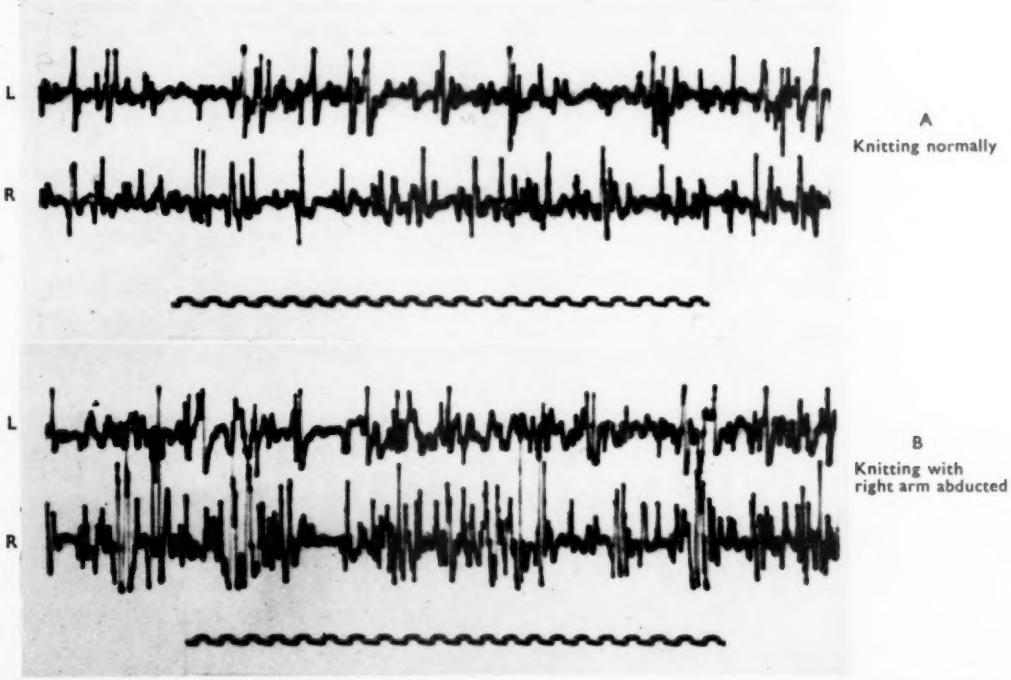


Fig. 4.—Simultaneous needle electrode recordings from symmetrical situations in the trapezii of a normal subject during knitting with right arm in normal position (A) and abducted (B).

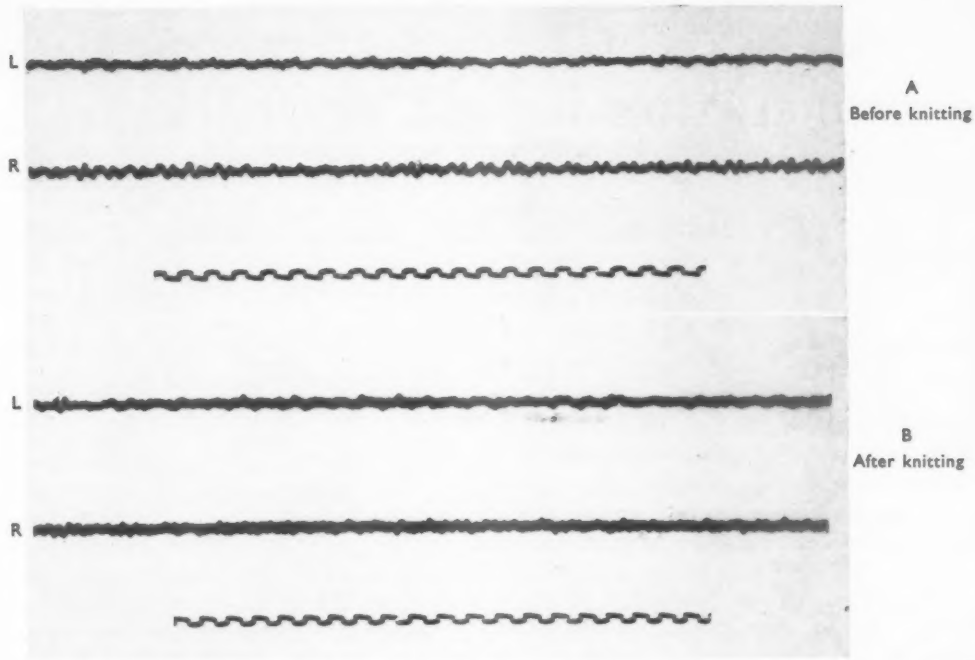


Fig. 5.—Similar needle positions to Fig. 4 to show electrical silence before knitting (A) and after knitting (B) when severe "fibrositic" pain had been induced on the right side.

theory that muscle spasm is the direct cause of somatic pain, in most cases at any rate. Tired muscles are painful, and in this sense pain in certain psychoneurotics may perhaps result from unnecessary or exaggerated muscular activity. In this connexion it may be of importance that tiredness and exhaustion are very common symptoms in these patients.

Summary

(1) The evidence supporting the concept of muscle spasm as a common cause of skeletal pain is reviewed.

(2) Similar sustained electrical activity is found in many painless conditions.

(3) The characteristic high frequency activity of painful muscular cramp is contrasted with the relative or complete electrical silence of the skeletal muscles in most somatic pains.

(4) An experiment is described in which "fibrositic" pain was induced without any electrical evidence of muscular spasm.

REFERENCES

Adams, R. D., Denny-Brown, D., and Pearson, C. M. (1953). "Diseases of Muscle". Cassell, London.

Bauwens, P. (1948). *Brit. J. phys. Med.*, **11**, 130.

Elliott, F. A. (1944a). *Lancet*, **1**, 47.

—— (1944b). *Annals of the Rheumatic Diseases*, **4**, 22.

Holmes, T. H., and Wolff, H. G. (1952). *Psychosom. Med.*, **14**, 18.

Richardson, A. T. (1951). *Arch. phys. Med.*, **32**, 199.

Rose, G. K. (1954). *Lancet*, **1**, 1143.

Schlesinger, E. B. (1946). *Bull. N.Y. Acad. Med.*, **22**, 520.

——, Drew, A. L., and Wood, B. (1948). *Amer. J. Med.*, **4**, 365.

Weddell, G., Feinstein, B., and Pattle, R. E. (1944). *Brain*, **67**, 178

Spasme musculaire comme cause de douleur somatique

RÉSUMÉ

(1) On passe en revue la conception du spasme musculaire comme cause de la douleur organique.

(2) On trouve une activité électrique soutenue similaire dans beaucoup d'affections indolores.

(3) On oppose l'activité caractéristique de haute fréquence de la crampe musculaire douloureuse au silence électrique relatif ou complet des muscles striés dans la plupart des douleurs organiques.

(4) On décrit une expérience dans laquelle on avait provoqué une douleur de "fibrosite" sans aucune manifestation électrique de spasme musculaire.

Espasmo muscular como causa de dolor somático

SUMARIO

(1) Se pasa en revista el concepto del espasmo muscular como causa de dolor orgánico.

(2) Actividad eléctrica sostenida similar fué encontrada en muchas afecciones sin dolor.

(3) Se contrasta la actividad característica de alta frecuencia del calambre muscular doloroso con el silencio eléctrico relativo o completo de los músculos estriados en la mayoría de los dolores somáticos.

(4) Se describe un experimento en que un dolor "fibrosítico" fué provocado sin manifestación eléctrica alguna de espasmo muscular.

CORRELATION OF THE ERYTHROCYTE SEDIMENTATION RATE AND GOLD COMPLICATIONS IN RHEUMATOID ARTHRITIS

BY

LENNART KALLIOMÄKI

Medical Clinic of the University, Turku, Finland

(RECEIVED FOR PUBLICATION JULY 5, 1954)

Certain observations have been reported according to which complications in association with gold therapy in rheumatoid arthritis would seem to be inversely proportional to the erythrocyte sedimentation rate (Goldie, 1939; Ellman and others, 1940; Lawrence, 1953). This has been explained on the basis that a high E.S.R. is generally seen in the active exudative stage of the disease, and that the gold, which has become bound to the globulins, is then able to penetrate through the damaged capillaries into the diseased tissue. Consequently the gold concentration in the skin, bone marrow, and other tissues is unable to attain the same levels as when the E.S.R. is low and the disease is in a less active stage.

Since this point is an important one in clinical practice, I have observed the possible correlation of gold complications and E.S.R. in patients receiving continuous gold therapy at the Turku Polyclinic for Rheumatic Diseases.

Material

The series comprised 173 patients. The gold* was administered once weekly during 10-12 weeks and the 50-mg. limit was not exceeded. When a total dosage of 500 mg. had been reached, further administration was in the form of a so-called maintenance dosage of 50 mg. once a month.

Results

The Table shows the correlation between the incidence of gold complications and the erythrocyte sedimentation rate. In those cases in which there were no complications of this kind, the lowest E.S.R. during gold therapy was noted. In cases with complications, the E.S.R. registered during the occurrence of the complication was observed. Without exception all onsets of dermatitis during the gold therapy were taken into consideration. Itching without dermatitis was not considered a complication. There were no cases of thrombocytopenia in our series.

TABLE

INCIDENCE OF GOLD COMPLICATIONS RELATED TO ERYTHROCYTE SEDIMENTATION RATE

Complication	E.S.R. ≦30 mm./hr.		E.S.R. >30 mm./hr.	
	No. of Patients	Percentage	No. of Patients	Percentage
Dermatitis	42	36·2±4·4	20	35·1±6·3
Eosinophilia (≧ 10 per cent.) ..	7	6·0±2·2	3	5·3±3·0
Leukopenia (≦ 3,000 leucocytes/c.mm.)	8	6·9±2·3	1	1·8±1·7
Proteinuria	7	6·0±2·2	2	3·5±2·4
Total Patients ..	116		57	

The Table shows that dermatitis occurring in association with gold therapy had no correlation with the E.S.R. In other words, the number of cases of dermatitis was equally high regardless of the level of the E.S.R. The same was also true of eosinophilic reactions. On the other hand, the cases with leukopenia (≦3,000/c.mm.) are seen to be more numerous in the group of cases with an E.S.R. of ≦30 mm./hr. Our material, however, is not sufficiently large to make this difference statistically quite definite (difference between percentages is 5·1±2·8). A grouping of the same type is also seen in the cases with proteinuria, although this shows no statistically definite difference.

Discussion

Evaluating the nature of gold complications on the basis of our series of cases, it would seem that dermatitis and eosinophilic reactions are chiefly of an allergic nature, and for this reason their incidence

* The gold preparation used in all cases was Myocrisin (May and Baker).

is the same, regardless of the stage of activity of the disease. This seems quite natural, since quantities have no bearing on the onset of an allergic reaction. On the same basis, leukopenia and proteinuria would be toxic conditions. In this light it would be readily comprehensible why these reactions appeared to be more frequent when the E.S.R. was low, and when, for the reason referred to above, the gold concentration in, for instance, the bone marrow and the kidneys was able to increase to a higher level than in the active phase of the disease.

Summary

The relationship between the erythrocyte sedimentation rate and complications during gold therapy were studied in 173 patients with rheumatoid arthritis. No correlation with the E.S.R. was seen in cases in which dermatitis or eosinophilic reactions developed during gold therapy, but the incidence of leukopenia and proteinuria was higher in patients with a low E.S.R. It is suggested that dermatitis and eosinophilic reactions should be regarded as chiefly allergic, whereas leukopenia and proteinuria are more in the nature of toxic reactions to the gold therapy.

REFERENCES

Ellman, P., Lawrence, J. S., and Thorold, G. P. (1940). *Brit. med. J.*, 2, 314.

Goldie, W. (1939). *Annals of the Rheumatic Diseases*, 1, 319.

Lawrence, J. S. (1953). *Ibid.*, 12, 129.

Rapport entre la vitesse de la sédimentation globulaire et les complications de la chrysothérapie dans l'arthrite rhumatismale

RÉSUMÉ

On étudia chez 173 malades atteints d'arthrite rhumatismale le rapport entre la vitesse de la sédimentation globulaire et les complications de la chrysothérapie. On ne trouva aucun rapport dans les cas de dermatite et d'éosinophilie survenant au cours du traitement par des sels d'or mais la leucopénie et la protéinurie furent plus fréquentes chez les malades à la vitesse de la sédimentation globulaire basse. On suggère que la dermatite et l'éosinophilie doivent être considérées comme réactions essentiellement allergiques tandis que la leucopénie et la protéinurie constituent plutôt des réactions toxiques à l'or.

Relación entre la velocidad de la sedimentación eritrocitaria y las complicaciones de la crisoterapia en la artritis reumatoide

SUMARIO

En 173 enfermos con artritis reumatoide se estudió la velocidad de la sedimentación eritrocitaria en relación a las complicaciones de la crisoterapia. No se encontró relación alguna en casos de dermatitis o de reacciones eosinofílicas ocurriendo durante el tratamiento por sales de oro, pero la incidencia de la leucopenia y de la proteinuria fué mayor en enfermos con velocidad de sedimentación baja. Se sugiere que la dermatitis y las reacciones eosinofílicas deberían considerarse como reacciones principalmente alérgicas, mientras que la leucopenia y la proteinuria representarían más bien reacciones tóxicas al oro.

"SCREENING" OF THE POPULATION FOR RHEUMATIC DISEASES*

BY

J. J. de BLÉCOURT

From the Centre for Rheumatic Diseases University Hospital, Groningen, Netherlands

(RECEIVED FOR PUBLICATION JULY 16, 1954)

The prevalence of rheumatic disorders has been investigated in the population of some villages in the northern part of the Netherlands.

Material

All these examined were over 14 years old, and lived in the village of Ten Boer, on the mainland of the province of Groningen, and in the villages on the Wadden-isles, Schiermonnikoog and Terschelling. To begin with, the people were informed verbally and in writing of the importance of the inquiry. The persons approached totalled 4,212 (567 from Schiermonnikoog, 791 from Ten Boer, and 2,854 from Terschelling); 80 per cent. (comprising 1,595 men and 1,783 women) responded, the greater part of the 20 per cent. who did not respond being prevented from doing so by reason of absence, sickness, etc.

The age structure of the population examined followed the usual pattern, except that the 14-20 year age group and also to some extent the 21-30 year and the 31-40 year groups were less well represented than usual. This can be attributed to the fact that many older persons return to Schiermonnikoog and Terschelling for their retirement, while young persons of between 14 and 30 years of age often leave these districts to pursue their studies or to engage in sea-going trade.

Method

The persons agreeing to participate were written to and called for interview street by street. The investigators (all specialists in rheumatology) questioned them and noted their replies according to a set formula. The questions concerned general health, presence of rheumatism (including its form and localization), time of onset, treatment and the results obtained, living conditions, working conditions, and the relation if any of these factors to rheumatism.

After the interview the cases were classified as negative or positive. The positive class included the following:

(*a*) Those suffering at the time from pain which could be attributed to rheumatic disease;
(*b*) Those who had suffered such pain in the previous year.

All other persons were classed as "negative". All "positive" cases were either examined immediately or referred with the agreement of their own general practitioner to a rheumatism clinic.

The value of this inquiry rests on the precision with which the questionnaires were completed and interpreted. There remains inevitably a certain element of subjectivity and superficiality, but it was found that as soon as the investigators had acquired a certain degree of skill each interview took only about 3 minutes and that very often the negative cases could be disposed of in a minute or so.

At Terschelling the inquiry was carried out in collaboration with the mass Radiography Unit of the Anti-Tuberculosis Campaign, and the co-operation between the two teams (both organized by the Green Cross) was excellent in both the preparatory and the interview stages. A single organization was concerned with the preliminary arrangements, and those concerned only had to attend once, which seemed to be much appreciated by the public.

Results

Among 3,378 persons interrogated, 621 (18·4 per cent.) were found to be suffering from rheumatic complaints (Table I). About 25 per cent. complained of "rheumatism", but after examination and diagnosis this was reduced to 18·4 per cent. The proportions of men and women classed as "positive" were 13·5 and 21·7 per cent. of the total; about 3·2 per cent. of them were found to be suffering from a rheumatic disease serious enough to require medical treatment; most of the rest were already under medical care.

Acute rheumatism (rheumatic fever) was diagnosed in 0·29 per cent., and rheumatoid arthritis and ankylosing spondylitis in 1·06 per cent. of the persons examined. Thus 1·35 per cent. of the whole

* This is a condensed account of the full report of this large-scale survey (de Blécourt and Basart, 1953, 1954).

population under review were suffering from the most serious forms of rheumatic disorder. About 60 per cent. of these were in need of medical treatment, while in the rest the disease was in remission.

TABLE I
PERCENTAGE AFFECTED WITH VARIOUS FORMS OF DISEASE

Complaint	No.	Per cent. of all Complainers		Per cent. of Total
Rheumatic fever	10	1·6		0·29
Rheumatoid arthritis	32	4·8		0·81
Ankylosing spondylitis	4	0·6	44·7	0·1
Osteo-arthritis	234	37·7		6·9
Rheumatism of the soft tissues	341	55·3		10·3
Total	621	100		18·4

In the positive group, 79·1 per cent. of the women and 84·5 per cent. of the men were over 40 years of age.

The proportion of sufferers from arthropathies was 44·7 per cent., and from rheumatism of the soft tissues 55·3 per cent. In women the latter often took the form of neuromyalgic symptoms in the cervico-scapular region, in men it most frequently presented as sciatic pain.

It is possible that fashions in dress are important factors among the women, and agricultural labour among the men.

No differences were noted between the inquiries carried out in July and those done in November, and there were no regional differences, though the figures were in every instance too small to allow definite statistical conclusions.

Discussion

The results of other investigators in Sweden, Denmark, and England correspond closely (Table II).

TABLE II
RESULTS COMPARED WITH THOSE OF OTHER INVESTIGATORS

Investigation	Present Study	Kalbak (1953)	Kellgren and others (1953)	Bohman (1948)
Country	Netherlands	Denmark	England	Sweden
Proportion of positive cases	18·4 per cent.	18 per cent.	19 per cent.	—
Sex ratio	13·5/21·7	—	16/21	—
Cases needing medical treatment	3·2 per cent.	9 per cent.	10 per cent.	3·8 per cent.
Total acute rheumatism, rheumatoid arthritis, and ankylosing spondylitis	1·35 per cent.	—	2·4 per cent.	1·9 per cent.

In Holland, as in Denmark and England, most of the sufferers (especially the men) were in the age group 41-60 years.

Our investigation also confirms the view of Kalbak (1953) that cervico-scapular rheumatic pain predominates in women and sciatic pain in men. On the other hand, whereas Kalbak found that 66 per cent. of rheumatic complaints were muscular and 34 per cent. articular, our figures are 44·9 per cent. articular and 55·1 per cent. muscular. This disparity and also the high incidence of cases of osteo-arthritis in our material is probably due to the higher average age of our cases.

All the houses occupied by the persons examined (a total of 2,638) were checked for their degree of dampness, using hygrometers specially designed for the purpose (the results of this study are reported elsewhere). Although most of the houses were damp, this did not seem to increase the frequency of rheumatic complaints to any appreciable degree; this is in agreement with the observations of Kellgren and others (1953) in England, and of Dahlberg and Grubb (1951) in Sweden.

Without giving too much importance to preliminary observations it appears that a useful method has been evolved for making a rough estimate of rheumatic morbidity in various areas of the country.

By analysing figures thus obtained in relation to those produced by other workers, it is possible to formulate conclusions about the need of clinics, and their number, nature, and location. A repetition of these inquiries after 5 or 10 years' work by such clinics will show whether or not they are useful.

When further inquiries on these lines have been carried out in other places, the influence on the rheumatic diseases of such factors as geographical location, occupation, climate, sex, etc., may be gauged more precisely. For this purpose this sampling process might be carried out in the same way throughout the country.

Summary

An investigation has been made of the incidence of rheumatic disease in a specified area of North Holland; 4,212 persons over the age of 14 were approached, and 3,378 (1,595 men and 1,783 women) came for interview; 621 (18·4 per cent.) were found to be suffering from some form of rheumatism, but most of these were not acutely affected at the time of the interview, the number seriously ill amounting to 1·35 per cent. of the 3,378 examined. Articular complaints accounted for 44·7 per cent. and muscular pains for 55·3 per cent. of those affected. The proportions of men and women affected were

13·5 and 21·7 per cent. respectively; 84·5 per cent. of the men and 79·1 per cent. of the women were over 40 years of age.

These results are compared with those of other investigators in Denmark, England, and Sweden.

REFERENCES

de Blécourt, J. J., and Basart, A. H. M. (1953). "Report No. 20 of the Research Institute for Public Health Engineering T.N.O.". The Hague, Netherlands.
———, ——— (1954). *T. Soc. Geneesk.*, **32**, 219.
Bohman, F. (1948). *Acta med. scand.*, **132**, 150.
Dahlberg, G., and Grubb, I. (1951). *Acta genet. statist. med.*, **2**, 42.
Kalbak, K. (1953). *Ibid.*, **12**, 306.
Kellgren, J. H., Lawrence, J. S., and Aitken-Swan, J. (1953). *Annals of the Rheumatic Diseases*, **12**, 5.

Recensement de la population à l'égard des maladies rhumatismales

RÉSUMÉ

On fit une enquête sur la fréquence de la maladie rhumatismale dans une partie determinée de la Hollande du Nord. On s'adressa à 4.212 personnes âgées de plus de 14 ans et 3.378 (1.595 hommes et 1.783 femmes) se présentèrent à l'entrevue. On trouva que 621 personnes (18,4 pour cent) furent atteintes d'une des formes de rhumatisme, mais chez la plupart d'entre eux l'affection ne fut pas aiguë au moment de l'entrevue, la proportion des malades graves étant de 1,35 pour cent des 3.378 sujets examinés.

Parmi les affectés on trouva que 44,7 pour cent présentaient des manifestations articulaires et 55,3 pour cent des douleurs musculaires. Les hommes et les femmes furent affectés en proportion de 13,5 et de 21,7 pour cent respectivement; 84,5 pour cent des hommes et 79,1 pour cent des femmes furent âgés de plus de 40 ans.

On compare ces résultats avec ceux obtenus par d'autres rechercheurs au Danemark, en Angleterre et en Suède.

Censo de la población respecto a enfermedades reumáticas

SUMARIO

Se investigó la incidencia de la enfermedad reumática en una parte determinada del Norte de Holanda. Se abordaron 4.212 personas de más de 14 años de edad y 3.378 (1.595 hombres y 1.783 mujeres) de ellas presentáronse á la entrevista. En 621 personas (18,4 por ciento) encontrose una de las formas de reumatismo, pero en la mayoría de ellas éste no fué agudo al tiempo de la entrevista, la proporción de los enfermos graves siendo el 1,35 por ciento de los 3.378 sujetos examinados.

De los afectados, el 44,7 por ciento tuvo manifestaciones articulaires y el 55,3 por ciento dolores musculares. El 13,5 por ciento de los examinados fueron hombres afectados y el 21,7 por ciento mujeres; el 84,5 por ciento de los hombres y el 79,1 por ciento de las mujeres tuvieron más de 40 años de edad.

Se comparan estos resultados con los obtenidos por investigadores en Dinamarca, Inglaterra y Suecia.

ROLE OF VARIOUS SURGICAL OPERATIONS IN THE HISTORY OF PATIENTS WITH RHEUMATOID ARTHRITIS

BY

LENNART KALLIOMÄKI

Medical Clinic of the University, Turku, Finland

(RECEIVED FOR PUBLICATION JULY 5, 1954)

Although the aetiology of rheumatoid arthritis still remains unexplained, it is known that a number of external circumstances of various kinds may be at least the apparent precipitating factor. Among such factors may be mentioned infections, traumata, confinements, etc.

The investigation by Edström (1951) on the correlation of trauma and rheumatoid arthritis is based on a study of 2,034 patients, in 72 of whom (3·5 per cent.) the onset of the disease occurred immediately following a trauma. The ratio between females and males was 15 : 57 among these 72 patients, whereas it was 66 : 33 in the total series. From this observation in particular Edström drew the conclusion that the development of the disease is not merely a chance occurrence and that trauma also plays an aetiological role. In studying the part possibly played by pregnancy and parturition, Oka (1953) based his observations on 732 female patients over 15 years of age, and arrived at the conclusion that the onset of rheumatoid arthritis during pregnancy or immediately thereafter is so common that under certain circumstances pregnancy and parturition can be considered as aetiological factors.

It was the object of the present study to examine the role of certain of the more common surgical operations in the history of patients with rheumatoid arthritis.

Material

The series comprised 187 female patients over 20 years of age, who underwent treatment for rheumatoid arthritis in the Turku Polyclinic for Rheumatic Diseases. Female cases only were included in this study in order that the material would be uniform in its relation to all the types of operation studied.

Results

The results of the inquiry are shown in the Table. Amputative gynaecological operations and thyroidectomies were the most prominent operations in the previous history of these patients. The ratio of thyroidectomies to appendicectomies and tonsillectomies in this series does not conform with the normal ratio, since, for instance, the Surgical Clinic of the Turku University performs yearly about 600 appendicectomies but only 100-150 thyroidectomies. The thyroidectomized group, furthermore, includes two patients in whom the operation could be considered to have had a definite aetiological role in rheumatoid arthritis, and two patients in whom the operation caused an exacerbation of this disease.

TABLE

INCIDENCE OF SURGICAL OPERATIONS IN 187 FEMALE PATIENTS WITH RHEUMATOID ARTHRITIS

Operation	Patients		Time of Operation		
			Before Onset	After Onset	
	No.	Per cent.		No Influence	Exacerbation
Uterus amputation Oophorectomy ..	8 2	5·3	5 2	3	
Thyroidectomy ..	10	5·3	8		2
Tonsillectomy ..	9	4·8	6	2	1
Appendicectomy ..	5	2·1	5		
Cholecystectomy ..	3	1·6	2	1	

Case Reports

Case 1, the 49-year-old wife of a policeman, underwent thyroidectomy in November, 1952. There had been symptoms of thyrotoxicosis for about 6 months previously. One month after the operation she began to feel tenderness in all joints and a typical case of rheumatoid arthritis developed.

Case 2, a housemaid aged 43, underwent thyroidectomy in 1938. In 1939 there was an onset of rather severe typical rheumatoid arthritis, which resisted all therapeutic measures. Symptoms of hypothyreosis began to appear at about the same time.

Case 3, shop assistant aged 56, developed typical rheumatoid arthritis in 1952. On her admission for treatment on July 15, 1953, active rheumatoid arthritis and also a large nodular goitre and obvious thyrotoxicosis were diagnosed. Gold therapy was immediately instituted but the patient reacted poorly. From September 12 to December 11, 1953, she received treatment at the hospital of the Rheumatic Diseases Foundation in Heinola. On discharge the joint processes were fairly quiet. However, as the symptoms of thyrotoxicosis became increasingly evident and cardiac insufficiency began to develop, thyroidectomy was indicated. The operation was performed in March, 1954, after which the heart and general physical condition improved, and her weight increased. One month later, however, a definite exacerbation of the rheumatoid arthritis occurred, and the erythrocyte sedimentation rate rose to 45-91 mm./hr. The patient had previously tolerated gold without any complications, but now even small doses (0·01 g.) produced leukopenia.

Case 4, a 34-year-old dressmaker, reported the onset of rheumatoid arthritis 7 years previously, and 3 years after that a pregnancy, during which all the joint symptoms disappeared. Thyroidectomy was performed in January, 1954, because of mild thyrotoxicosis, and 3 weeks after the operation there was a sudden onset of very active rheumatoid arthritis, and typical symptoms of hypothyreosis appeared simultaneously.

No time correlation could be seen between the other surgical operations and the onset of rheumatoid arthritis in these four patients.

In order to study the incidence of uterus amputations, oophorectomies, and thyroidectomies in a control series of patients not affected by rheumatoid arthritis I collected from the Medical Clinic of the Turku University a series of 150 female patients over 20 years of age who were hospitalized for various infectious diseases, hypertension, and degenerative heart disease. The gynaecological operations mentioned had been previously performed in eight (5·3 per cent.) and thyroidectomy in three (2 per cent.). The history of the rheumatoid arthritis and control series was thus similar as regards gynaecological operations, but thyroidectomy was more frequent in the history of the rheumatoid arthritis patients. The difference is not statistically significant (difference $3 \cdot 3 \pm 1 \cdot 9$), though the opinion that thyroidectomy may influence the onset or exacerbation of rheumatoid arthritis is borne out by the four cases described above.

It seems probable that the thyroid also affects the development of rheumatoid arthritis in other ways. Experimental studies (Selye and others, 1944; Harrison and Barnett, 1953) and clinical investigations (Stepantschitz and Schreiner, 1952) are in favour of this opinion. In weighing the indications for thyroidectomy in a patient with rheumatoid arthritis, consideration should be given to the possible aggravating effect of the operation on the course of the joint disease. Before a diagnosis of thyrotoxicosis is made in a patient with rheumatoid arthritis it should be remembered that the latter disease may simulate the symptoms of thyrotoxicosis (tachycardia, sweating, psychic lability, etc.). It is obvious, of course, that if a definite diagnosis of thyrotoxicosis is made in an arthritic patient, the thyroid disease must be treated first, since thyrotoxicosis is a graver condition prognostically than rheumatoid arthritis.

Summary

(1) A study was made of the role of certain surgical operations in the history of 187 female patients with rheumatoid arthritis.

(2) Uterus amputation and oophorectomy had been performed in 5·3 per cent. of these cases, and the incidence was the same in a control series. Thyroidectomy had been performed in 5·3 per cent. of the rheumatoid arthritis patients and in only 2 per cent. of the control cases (difference $3 \cdot 3 \pm 1 \cdot 9$). Other studied operations noted were appendicectomy in 2·1 per cent., tonsillectomy in 4·8 per cent., and cholecystectomy 1·6 per cent.

(3) In two cases of previous thyroidectomy a definite correlation was evident between the surgical operation and the onset of rheumatoid arthritis. In two other cases exacerbation of the joint disease immediately following thyroidectomy was clearly demonstrable. No time correlation was seen between the other operations studied and the onset or course of rheumatoid arthritis.

(4) It is pointed out that thyroidectomy should be performed on patients with rheumatoid arthritis only when there are grave indications for the operation.

REFERENCES

Edström, G. (1951). *Rev. Rhum.*, **18**, 507.
Harrison, R. G., and Barnett, T. J. (1953). *Annals of the Rheumatic Diseases*, **12**, 275.
Oka, M. (1953). *Ibid.*, **12**, 227.
Selye, H., Sylvester, O., Hall, C. E., and Leblond, C. P. (1944). *J. Amer. med. Ass.*, **124**, 201.
Stepantschitz, G., and Schreiner, B. (1952). *Wien. klin. Wschr.*, **64**, 981.

Role de différentes opérations chirurgicales dans l'histoire des malades atteintes d'arthrite rhumatismale

RÉSUMÉ

(1) On étudia le rôle de certaines opérations chirurgicales dans l'histoire de 187 malades atteintes d'arthrite rhumatismale.

(2) L'hystérectomie et l'oophorectomie fut effectuée dans 5,3 pour cent des cas; le pourcentage de ces opérations chez les témoins fut similaire. La thyroïdectomie fut effectuée dans 5,3 pour cent des cas d'arthrite rhumatismale et chez 2 pour cent seulement des témoins (différence $3,3 \pm 1,9$). D'autres opérations notées furent: appendicectomie chez 2,1 pour cent, amygdalectomie chez 4,8 pour cent et cholecystectomie chez 1,6 pour cent.

(3) Dans deux cas de thyroïdectomie antérieure un rapport défini entre l'opération et le début de l'arthrite rhumatismale fut évident. Dans deux autres cas l'exacerbation de la maladie articulaire immédiatement après la thyroïdectomie fut clairement démontrable. On n'observa pas de rapport de temps entre les autres opérations étudiées et le début ou l'évolution de l'arthrite rhumatismale.

(4) On fait remarquer que la thyroïdectomie n'est indiquée chez les rhumatisants que pour des raisons graves.

El papel de varias operaciones quirúrgicas en la historia de enfermas con artritis reumatoide

SUMARIO

(1) Se estudió el papel de algunas operaciones quirúrgicas en la historia de 187 enfermas con artritis reumatoide.

(2) La histerectomía y la ooforectomía fueron efectuadas en el 5,3 por ciento de los casos, con el número similar de tales operaciones en los testigos. El 5,3 por ciento de las enfermas reumáticas y tan sólo un 2 por ciento de los testigos (diferencia $3,3 \pm 1,9$) fueron tiroidectomizadas. Otras operaciones notadas fueron: apendicectomia 2,1 por ciento, amigdalotomía 4,8 por ciento y colecistectomía 1,6 por ciento.

(3) En dos casos de tiroidectomía anterior una relación determinada entre la operación y el comienzo de la artritis reumatoide fué evidente. En dos otros casos la exacerbación de la enfermedad articular inmediatamente después de la tiroidectomía fué claramente demostrable. No se observó relación alguna de tiempo entre las demás operaciones estudiadas y el comienzo o la evolución de la artritis reumatoide.

(3) Se hace observar que la tiroidectomía en enfermos con artritis reumatoide se debe efectuar tan sólo en caso de indicación grave.

AMERICAN RHEUMATISM ASSOCIATION

PROCEEDINGS OF THE ANNUAL MEETING, 1954

The annual meeting of the American Rheumatism Association was held at San Francisco, California, on June 18 and 19, 1954, under the presidency of Dr. Charles Ragan of New York. The presidential address, the interim report of the A.R.A. Cooperative Study of Cortisone Therapy, and abstracts of thirty papers with the discussions thereon are printed below.*

Presidential Address

BY

CHARLES RAGAN

President, American Rheumatism Association, 1953-54

Since the end of the second world war, the American Rheumatism Association has experienced a phenomenal growth in membership, in total number as well as in those participating actively at meetings. The physical size of the programme has grown, and it seems fair to say, without false pride, that the character of the programme has improved remarkably. The papers presented show more interest in basic problems and an increasingly careful evaluation of therapeutic agents. Young men have entered the field in larger numbers than could have been anticipated in the past, and in many instances, through support from the United States Public Health Service or the Arthritis and Rheumatism Foundation, they have provided themselves with a solid background of basic science upon which to build in the future. This we may regard as sound achievement. On the other side of the ledger, we have only to look at one of our major problems—rheumatoid arthritis—to realize that we have yet a long way to go. We continue to be in the dark concerning the origin and progression of this disease, and its course may only be predicted on a statistical basis, although our knowledge of the tissues and the changes induced by the disease has unquestionably advanced. There is, I believe, reason for this dichotomy. It is obvious that no one has a clear-cut idea for a direct approach to the core of the problem of rheumatoid arthritis, and investigation has, perforce, been pursued at the periphery through indirect paths.

So much for the past. What directions should we take? We, in the American Rheumatism Association, have two aims in our efforts to do the best for our patients: to increase our knowledge, and to add to the number of physicians competent to carry out this care. To achieve this, new men of competence, dedication, integrity, and originality are our crying and continuing need. A young man in medicine is attracted to some particular area by natural interest, by the possibility of advancing knowledge, or perhaps unfortunately by the chance of assured security. The popular and fashionable areas of interest in the past have been largely those in which answers might be readily obtained by the investigator or in which the clinician might reasonably anticipate a prompt and successful resolution of the patients' problems. For us in this Association, there appear to be few areas of research in which a quick answer can be foreseen by the investigator; the clinician confronted with the management of a rheumatic problem is aware that he faces long periods of sustained and often frustrating effort. Thus, there are currently no easy answers to our questions, either in the field of investigation or in clinical management. The gratifications derived from the care of the patient with a protracted illness are intangible, and research in which one nibbles away at the periphery of a clinical problem seldom yields the pleasure which comes from the direct conquest of disease. The field of rheumatism does not much appeal to young men, in contrast to such a specialty as haematology —in which recent rapid progress has opened up alluring vistas.

The roundabout attack on our problems, enforced by necessity, has led to another difficulty in the recruitment of younger men. As I have said, the clinical care of the rheumatic patient is not easy, and to be adept in it, one frequently must combine the skills of the internist, the psychiatrist, and the physiatrist, as well as the endocrinologist and medical orthopaedist. This makes for a compleat family physician. In the clinical investigation of the rheumatic diseases, each of these disciplines may

* There were also panel discussions on "Hormones in Rheumatic Disease" (Moderator: R. H. Freyberg) and "Rehabilitation of the Arthritic Patient" (Moderator: E. W. Lowman).

as well need to be pursued. Clinical studies may have gone as far as they can in explaining the mysteries facing us. Various appendages to our major problems can still be studied, but a frontal attack can hardly be expected to be successful solely through further clinical approaches. Thus, the impetus has been towards experimentation on a more fundamental plane, and research has recently been directed towards expending our knowledge of the tissues involved, chemically, morphologically, embryologically, and in their reactions to trauma. Such investigations require not only intense and continuing training in fundamental science but also long periods of time for their completion. The time factor alone leads to difficulty by competing with the time required to become a compleat family physician. Even if we exclude interest, training, and aptitude, the time-factor allows only the very rare individual to become expert both clinically and in investigation. If the average physician is to be a competent clinician, there is just not time for him to become expert in the complexities of modern investigative procedures as well.

How can we best recruit individuals combining the two necessary types of ability at our present stage of maturity? I believe the answer lies in the teacher in the medical school with an interest in rheumatism. He must be a clinician as his area of instruction lies in clinical medicine and students rightly expect this. Since time permits only in rare instances, the perfect combination of compleat clinician and fundamental investigator, in the medical educator, clinical interest should predominate. This teacher, however, must have a critique in related fundamental problems to retain the respect of the student whose prior training has acquainted him with the basic approaches. He must make an effort to propound our problems to students using the mechanistic philosophy of disease, as the student has properly been led to expect this approach in other areas of medical education.

The importance to us of the medical educator with an interest in the rheumatic diseases cannot be over-emphasized. New blood must be infused into an organization continually if it wishes to retain its vitality, and this new blood must be good. It has to come from the young medical student whose first impressions are received from his teachers. If, because of sloppy thinking, these young ones are repelled, a field of medicine may be closed to them regardless of later attractions. The time when the student first comes to grips with a patient is a critical period of crystallization in which his future plans can be greatly affected. As Dr. Dietrich pointed out last November, the medical curriculum is full to overflowing, and the demands of the many pressure groups urging their special interests in medical education cannot be granted. I frankly admit we are one of these pressure groups; we believe that, within the limits of time and the mental capacity of the student, only a concept of our problems can be presented during the period of undergraduate instruction. The fruits of current basic research may in the foreseeable future find application in a mind prepared by a teacher of broad horizons. Above all, the student should not be repelled by loose uncritical thinking on our part; to exert influence on the highly intelligent body of undergraduate medical students, the inspiring teacher must exhibit depth as well as breadth. In graduate instruction—at the intern and resident level—we can hope to attract the individual more specifically to a given field of interest. Most forms of *post-graduate* medical education fail to draw individuals who may be counted upon to make significant contributions to the field. Post-graduate education does help greatly in instruction for the adequate care of patients suffering from the diseases which are our special concern, but I doubt that our knowledge will be increased by sparks struck in post-graduate education.

Being a clinician at heart, I believe that the greatest need is to continue to replenish the ranks of clinicians in the rheumatic diseases interested and disciplined in basic approaches, but I am not sure how we can attract people to work upon the fundamentals from which I am sure our answers will come. With the present emphasis on categorical grants for the study of disease, the clinician with basic orientation is in the driver's seat as the responsible investigator. My plea is for an assured method by which a continuing supply of enthusiastic, able young men may be attracted to the work of the Joint Chiefs of Staff. The burden rests on the shoulders of the teacher of undergraduate medical students. May I say that I do not mean myself, for I entered the field too early to be a compleat family physician and inspirer of young men, and have spent my declining years attending committee meetings rather than stimulating youth. The man who will lead medical students and house physicians through the intricacies of the rheumatic diseases with enthusiasm and integrity is the person to be fostered and nurtured.

If I have made my point that we need more men from this Association in the field of medical education at the undergraduate level, I should like to conclude by stating my personal opinions on how this can be achieved. The trend in medical education since the 1920s has been towards the full-time department, either strict or geographic. The

teacher is undoubtedly more available to the student if there is a close geographic proximity. *Availability* is a *sine qua non*. The distinction between strict and geographic full-time is solely a financial one, and in most schools, strict full-time, although permitting a greater degree of availability, is seldom economically feasible. For geographic full-time, as you know, part of the income is derived from salary and part from practice. The medical schools with their sadly depleted coffers can hardly be expected to provide this salary, which will have to stem from an interested agency—either voluntary or governmental. The concept of teaching grants used in other fields by the National Institutes of Health would answer our problem of teachers and ensure their availability to students, and the attractions of the challenge of the rheumatic diseases would be carefully propounded to the young in medicine. If these ends could be attained, we could be assured that this organization would continue as an active, living force, and that patients suffering from the rheumatic diseases would be cared for with competence and understanding.

Observations on the Antiphlogistic Influence of Adrenocortical Steroids. By THOMAS F. DOUGHERTY, *Salt Lake City, Utah.* (By invitation.)

It is now recognized that ACTH, cortisone, hydrocortisone, and certain other adrenocortical steroids have the capacities to moderate the inflammatory response to a wide variety of inflaming stimuli. In our laboratory we have attempted by various techniques, which will be described, to analyse this antiphlogistic effect. It was found that a close interrelationship exists between the amount of inflaming stimulus and the amount of cortisone or other antiphlogistic hormones required to diminish the inflammatory response. It may be concluded that when the inflammatory stimulus is constant, the degree of suppression of the inflammation is directly proportional to the amount of antiphlogistic hormone given. When the intensity of the stimulus is increased within certain limits this same linear relationship holds constant. The greater the stimulus at any localized site, the greater is the amount of antiphlogistic hormone needed to suppress the inflammation, and *vice versa*. The experiments to be discussed indicate that not only is there a graded requirement of cortisone in inflamed tissue, but also that the hormone does not act through some general systemic mechanism, but rather exerts its antiphlogistic effect directly at the site of the inflammation.

Investigations have been made in this laboratory on the effects of hydrocortisone and C^{14}-labelled hydrocortisone on changes in ground substance and fibroblasts as observed by electron microscopy and histochemical and radio-autographic techniques.

Role of the Adrenal Cortex in Homeostasis. By DWIGHT J. INGLE, *Chicago, Ill.* (By invitation.)

The secretory capacity of the adrenal cortices is very great and varies in response to changes in "need" during different degrees of stress.

During severe stress, some of the metabolic changes resemble those caused by the administration of large amounts of cortical hormones or ACTH. It has been postulated that a number of the metabolic changes associated with stress are due to the increased secretion of cortical hormones. In some instances this seems to be true. The regression of lymphoid tissue and the reduction in blood lymphocytes and eosinophils during stress are apparently due primarily to the increased output of hormone by the adrenal glands. On the other hand the cortical hormones may be essential for the full manifestation of a metabolic response to stress, although a change in secretory activity is not required. As an example, the rise in urinary non-protein nitrogen which characteristically follows a fracture is not manifest in the untreated adrenalectomized rat but does occur in similar animals treated with a constant intake of adrenal cortex extract. In these experiments, an increased output of cortical hormones was not a factor in stimulating catabolism—adrenal cortices were absent.

Since an excess of the cortical steroids will intensify diabetes in the partially depancreatized rat, and since it is known that any stress causes an increased secretion of cortical hormones, it might be expected that a stress would also intensify the glycosuria of mildly diabetic rats. On the contrary, the injection of toxic doses of formaldehyde into such animals caused some decrease in glycosuria. When these experiments were repeated on adrenalectomized-depancreatized rats in which the preadrenalectomy level of glycosuria was sustained by a constant intake of adrenal cortex extract, the administration of formaldehyde caused a still greater decrease in glycosuria. It was concluded that, during this stress, the rats having intact adrenal cortices were better able to sustain homeostasis by increasing their output of cortical steroids in response to this increased need. Whereas a similar increased output of cortical hormones in the absence of a "need" would exacerbate the diabetes, the response during stress simply prevents the cortical insufficiency that would otherwise ensue and tends to sustain homeostasis rather than to disturb it.

Growth-Hormone-Induced Osteo-Arthropathy. By C. W. ASLING, M. E. SIMPSON, H. D. MOON, C. H. LI, and H. M. EVANS, *San Francisco, Calif.* (Read by Dr. Simpson.)

Roentgenographic and histologic studies have been made on the skeletons of fifteen intact and thirteen hypophysectomized adult female rats which received injections of anterior hypophyseal growth hormone (electrophoretically homogeneous) for over a year, in dosages as high as 3 mg. daily. Control groups of fifteen intact and ten hypophysectomized rats were injected with serum albumin.

Joint abnormalities observed in the injected rats involved the knee, ankle, and vertebral column. Changes in the knees and ankles were almost always symmetrical and of equal severity bilaterally. Their roentgenographic appearance was similar to that described by

Reinhardt and Li (1953)* in growth hormone treated adrenalectomized rats. No other joints appeared to be affected. None of the controls showed similar disorders. The deformities resulting from injections were more frequent and more severe in hypophysectomized rats.

Histological changes at the knee joint consisted of irregular articular surfaces, thickened joint linings, and excessive, irregular osteogenesis. At the ankle joint the changes consisted of excessive, irregular bony outgrowths of tibia, fibula, and calcaneus, thickened joint linings, and occasional erosion of articular cartilage. In the vertebral column, the commonest change was excessive bony growth on the ventral aspect of vertebral bodies and change in shape of intervertebral spaces.

Rate of Disappearance from Plasma of Cortisone and Hydrocortisone. By RALPH E. PETERSON, SERAFIM L. GUERRA, JAMES B. WYNGAARDEN, BERNARD B. BRODIE, and JOSEPH J. BUNIM, *Bethesda, Md.*

Knowledge of the physiological disposition of cortisone and hydrocortisone should afford a rational basis for dosage schedule of these compounds and might lend a better understanding of the apparent merits of one steroid as compared with the other. Heretofore, no information has been available on the relative rates of disappearance of the steroids from plasma in normal subjects and in patients with disease.

Cortisone and hydrocortisone were administered intravenously to normal subjects and the rates of disappearance from plasma were determined. The analytical method employed was a modification of the method of Silber, involving extraction of steroids into methylene chloride and reaction with phenylhydrazine in sulphuric acid. The steroids were given as 100 or 200 mg. crystalline free alcohol (Merck) in 500 ml. water containing 5 per cent. dextrose and 1·5 per cent. ethanol over a 30-minute period. Counter-current distribution studies on the methylene chloride extract of plasma obtained 100 minutes after the infusion of hydrocortisone have shown that more than 90 per cent. of the steroid assayed as the phenylhydrazone is identical with hydrocortisone. The mean biologic half-life for hydrocortisone in normals was found to be 115 minutes, whereas cortisone disappeared from plasma approximately twice as rapidly, with a half-life of 65 minutes. Calculation of the volumes of distribution indicate that both steroids are distributed roughly throughout the total body water. In patients with liver disease, hydrocortisone disappears from plasma at a rate up to four times slower than normal, whereas cortisone disappears at the normal rate. It may be that the ameliorating effect of jaundice on rheumatoid arthritis is related to the slow rate of metabolic transformation of the hydrocortisone normally elaborated by the adrenal cortex. The plasma clearance rates of cortisone and hydrocortisone in patients with rheumatoid arthritis are being determined at present.

Discussion.—DR. PHILIP S. HENCH (*Rochester, Minn.*): May I express my admiration for this excellent paper. Studies such as this demonstrate how the cortisones are metabolized by normal and by rheumatoid persons. None of these patients had jaundice. It would be most interesting to see whether the cortisones were metabolized differently by rheumatoid patients with and without intercurrent jaundice. Such a study might help to determine whether or not hydrocortisone is the antirheumatic substance X of jaundice.

* Reinhardt, W. O., and Li, C. H. (1953). *Science*, 117, 295.

Metabolism of Adrenal Cortical Steroids in the Synovial Cavity in Rheumatoid Arthritis. By HILDEGARD WILSON, RICHARD FAIRBANKS, CURRIER MCEWEN, and MORRIS ZIFF, *New York City, N.Y.*

The peripheral metabolism of cortisone and hydrocortisone in inflamed tissue has been investigated to gain insight into the mechanism of their anti-inflammatory activity. The following evidence for the local transformation of injected corticosteroid by rheumatoid synovial tissue has been obtained. Chromatographic analysis of post-injection synovial fluid showed substantial amounts of a number of metabolites of intra-articularly injected cortisone and hydrocortisone. Only trace amounts were found when the uninjected contralateral knee was aspirated at the same time, indicating local metabolism, since if metabolites had been formed elsewhere they would have returned in more nearly equivalent concentrations to each side.

Both steroids yielded products of greater and lesser mobility, indicating that the tissue was capable of effecting a variety of metabolic transformations. A different pattern of metabolism was found for each steroid. Cortisone (locally inactive) yielded hydrocortisone, several other corticosteroids, and an abundant non-corticosteroid component. Hydrocortisone (anti-inflammatory in the joint) gave rise to at least three other corticosteroids, 11β-hydroxy-Δ^4-androstene-3, 17-dione, and another 17-ketosteroid. The difference in metabolic pattern, together with the presence of relatively large amounts of hydrocortisone after cortisone injection, raises the question whether the unique anti-inflammatory effect of hydrocortisone in the synovial cavity lies in its transformation into a specific metabolic product.

Discussion.—DR. JOSEPH L. HOLLANDER (*Philadelphia, Pa.*): I should like to congratulate Dr. Wilson and her colleagues on their wonderful paper. The experimental data and the conception of the experiments are very good.

We have been using a slightly different approach in trying to find out how hydrocortisone works in the joint. Our work ties in very closely with the work of Dr. Dougherty which you heard earlier.

We find no disagreement with Dr. Wilson's results and wish only to commend them. Our only slight difference is in how some of the results are interpreted.

First of all, mention is made of conversion of cortisone to hydrocortisone in the joint. We found that also. Of our 26 cases, however, we found it in only one, in a patient who also got 24-hour clinical relief in the inflamed joint from an injection of cortisone. As you know, this happens in only a small percentage. I wonder if some people are able to convert cortisone to hydrocortisone in their tissues, and others not.

Our difference in approach might be likened to the difference between trying to find out what a family eats by looking in the refrigerator or by looking in the garbage can. In other words, if we try to discover where the injected material is stored and what it is like when

stored, we may, perhaps, reach one conclusion indirectly. If we "look in the garbage can" at what is not absorbed from this synovial fluid, we may infer the "diet" of the synovial tissue from that also.

Much of the injected hydrocortisone acetate or any other esters we have tested, is absorbed by the synovial fibroblasts, or at least into the synovial lining. We have not proved, as Dougherty has, that hydrocortisone goes into the fibroblasts, but we certainly agree. By taking synovial biopsies at various intervals after injection, we have shown that the hydrocortisone is stored in the synovium *as the ester*: in other words, the ester is *not* split off.

Therefore, we have assumed that, at least in storage before the hydrocortisone is actually used, it exists as the ester. We differ in the way we interpret these changes. We do not feel that the metabolite of hydrocortisone is *necessarily* the active agent, but that hydrocortisone itself may still be the active agent.

DR. EDWARD W. BOLAND (*Los Angeles, Calif.*): The data presented in the last two papers are highly significant. It may be hoped that through investigation of this type the reasons for differences in potency between the glycogenic adrenal cortical steroids, as well as their various esterified preparations, will be clarified. Indeed, the assayists are to be complimented.

From comparisons of clinical responses to oral administration, we are convinced that hydrocortisone (free alcohol), cortisone (free alcohol), hydrocortisone acetate, and cortisone acetate exhibit definite differences in antirheumatic potency. Differences in solubility of the compounds, or of the relative weights of the active principle in the case of esters, do not fully explain the divergencies. The data presented may imply that variances in rates and modes of metabolism and in survival times following absorption are also important.

To complicate the issue further, it may be appropriate at this time to relate some very preliminary observations which Dr. Headley and I have made with one of the halogenated derivatives of hydrocortisone, 9-alpha-fluoro hydrocortisone acetate.* To date we have administered this preparation for brief periods of days to only three patients—each with rheumatoid arthritis. No conclusions can be drawn from these pilot trials, but, to us, some of the observations are very interesting.

In animals, 9-alpha-fluoro hydrocortisone has high glycogenic activity and displays strong sodium-retaining properties. Acute toxicity studies have shown that it is not lethal to mice in dosages up to 1,000 mg./kg. Dr. George Thorn and his group have found the derivative extremely effective in maintaining patients with Addison's disease; as sole treatment, dosages of 0·25 to 0·5 mg. 9-alpha-fluoro hydrocortisone per day have been sufficient. Based on electrolyte studies, suppression of 17-ketosteroid excretion, and eosinopenic response, it is my understanding that Dr. Thorn has estimated that the compound is at least 25 times as potent, by weight, as cortisone, and that its efficiency in Addison's disease is comparable with that of aldosterone (electrocortin).

In the three patients to whom we administered 9-alpha-fluoro hydrocortisone acetate, rheumatoid activity was graded as severe, moderately severe, and moderate, respectively. The drug was given orally in divided doses of 1 mg. each, the initial total daily dosage being 4 mg. in one patient and 6 mg. in the other two. These small doses were prompted by Dr. Thorn's observations and animal studies which suggested a high degree of potency. The patients had received no recent treatment of significance beforehand and no auxiliary measures were employed except salt-poor diets.

Improvement in the articular manifestations began within 6 hours of the first dose (total 2 mg.) in two patients, and within 17 hours (total 3 mg.) in the other. The patient with severe disease had been confined to bed, unable to feed herself, or to reach for the telephone. She was able to sit in a chair after 2 days, to walk to the bathroom after 4 days, and to walk about the room without pain on the sixth day. The erythrocyte sedimentation rate (Westergren) dropped progressively in 8 days from 96 to 29 mm./hr. Similar, though less dramatic, improvement was seen in the other two patients and the response seemed to compare favourably with that noted from the much larger suppressive doses required with hydrocortisone and cortisone.

We have no data regarding adverse reactions. So far there have been none, but from available data regarding the compound's physiologic activity, they should be anticipated, particularly salt-and-water retention.

9-alpha-fluoro hydrocortisone acetate seems to possess striking antirheumatic activity and that its potency per milligram may be many times that of hydrocortisone and cortisone. If further investigations bear out this impression, a greater impetus may be provided for trials of other analogues or derivatives of hydrocortisone, in the hope that one with wide dissociation between anti-inflammatory and other unwanted physiological actions will eventually be found. The effectiveness of 9-alpha-fluoro hydrocortisone in such small doses would imply that certain properties of hydrocortisone can be changed by a relatively minor modification of its chemical structure.

DR. THEODORE B. BAYLES (*Boston, Mass.*): As usual the patients in Boston seem more resistant to cortisone and its analogues. In collaboration with Dr. George W. Thorn's group, we have treated two patients with active rheumatoid arthritis with fluoro hydrocortisone provided by Squibb and Company. When we gave a single 5-mg. dose by mouth, there was very little antirheumatic effect apart from a slight drop in the sedimentation rate. The response to 5 mg. twice a day orally seemed equivalent in antirheumatic effect to 75-100 mg. a day of cortisone. The patients were maintained in the Robert Breck Brigham Hospital on a rigid, low sodium diet of 1 g. or less, and 3 g. potassium chloride daily. Fluids were unlimited. One patient was a 62-year-old woman with auricular fibrillation and arteriosclerotic heart disease, and the other a young man aged 19 years. Up to the present time on the 5-mg. twice a day dosage, neither patient has shown fluid retention or other mineralocorticoid effects of an unpleasant nature. Certainly such limited experience allows no significant conclusions at the present time, except that this analogue is probably 7 to 10 times as effective antiphlogistically as cortisone.

DR. JOSEPH J. BUNIM (*Bethesda, Md*): I did not include some data in my paper because of time, but, in view of Dr. Boland's and Dr. Bayles's remarks it may be pertinent. We administered orally to normal subjects 300 mg. hydrocortisone (free alcohol); in a second experiment, 300 mg. cortisone (free alcohol); in a third, 300 mg. cortisone acetate; in a fourth, hydrocortisone acetate.

It is interesting to see what the peak concentration in the blood was at the end of 8 to 12 hours. The time interval varied from one experiment to another. Hydrocortisone (free alcohol) reached a peak level of thirty

* See page 291 for full article.

times the normal concentration in the blood (300 μg. as against the normal 10 μg.).

The same dose of cortisone (free alcohol) given by mouth caused a peak concentration of 200 μg. per cent., the same dose of cortisone acetate reached a peak of ten times the normal, 100 μg. per cent. The same dose of hydrocortisone acetate made practically no impression at all on blood concentration.

We have also studied antirheumatic and certain metabolic effects of fluorohydrocortisone in one patient. This was a white female patient aged 52, with rheumatoid arthritis of 25 years' duration, whose cortisone needs were well-known. She was allowed to have a flare of her arthritis by lowering the dose of cortisone from 75 to 50 mg. per day. She was then given 1 mg. fluorohydrocortisone per day in addition to the 50 mg. cortisone. No improvement resulted and the dose of fluorohydrocortisone was increased to 5 mg. per day. She then had a definite, but incomplete, response, and became about as well as she had been on the 75 mg. cortisone alone, in that she had less pain and less tenderness and slightly less swelling of her joints than she had at the beginning of this study. Then the cortisone was tapered and discontinued completely, but the fluorohydrocortisone was continued at 5 mg. per day. With this change in therapy, the patient had a marked increase in her symptoms and became worse than she had been on 75 mg. cortisone alone. During this time she was on a constant fluid, caloric, and sodium intake, consisting of 2 g. sodium per day. The urinary sodium showed an abrupt fall when the fluorohydrocortisone was started, the haematocrit fell from 37·5 to 31·5, her weight rose from 71·8 to 75·7 kg. in 14 days of therapy, and she developed massive oedema of her extremities. In this study no definite antirheumatic effect of fluorohydrocortisone alone was demonstrated, but it was found that combined fluorohydrocortisone and cortisone had an enhanced antirheumatic effect; 5 mg. fluorohydrocortisone seeming to be equivalent to about 25 mg. cortisone. A marked sodium-retaining effect of the drug was demonstrated.

DR. WILSON: We are aware of Dr. Hollander's very interesting experiments. Our studies differed in that we used cortisone and hydrocortisone free alcohols, rather than the acetates. We agree that all patients probably do not convert cortisone to hydrocortisone. In our previous report* one patient appeared to have converted cortisone acetate to tetrahydrocortisone.

It is certainly important for us to know more about the chemical interrelationships between the steroid hormones injected intra-articularly, and the compounds taken into the living tissue and the blood. This is obviously a complex subject. For one thing, the type of metabolite one finds depends on the time interval after injection at which fluid is withdrawn and analysed. We found quite a different pattern 3 hours after hydrocortisone from that seen after 30 minutes.

Another word of caution might be interposed regarding the difficulty of actually identifying a corticosteroid compound. Parallel mobility on paper chromatograms, even when there are other similarities to a known substance, do not necessarily prove the identity of an unknown. We have seen that cortisone and hydrocortisone are rapidly transformed in the synovial cavity, and that some of the products may retain certain properties of the original hormone. So it seems that a good deal of work lies ahead of us before we can define the nature and amounts of the steroids present at any one time, or relate our findings to the mechanisms of their anti-inflammatory effects.

* *Proc. Soc. exp. Biol.*, **83**, 648 (1953).

Interim Report of the American Rheumatism Association's Committee for the Cooperative Study of Cortisone Therapy in Rheumatoid Arthritis

Presented by

DR. CURRIER MCEWEN

Chairman of the Committee

This is the second report of this study involving the cooperative effort of 25 clinics in the United States and Canada and made possible by a grant from the Arthritis and Rheumatism Foundation. It is emphasized that this is not a "forward moving" study, but an analysis of clinic records of the judgment of physicians as to the effect of cortisone administration in individual patients. These effects are not compared with those induced by any other agent.

Records of 546 patients with rheumatoid arthritis have been analysed (63 per cent. females, 37 per cent. males). At the start of cortisone therapy, 25 per cent. had had the disease less than 3 years, 50 per cent. less than 7 years, and 75 per cent. less than 12 years. At the end of the 3-year period of study 432 (79 per cent.) were still under observation, 85 (15 per cent.) had left the study, and 29 (5 per cent.) had died. Of the 432 patients still under observation, 252 (58 per cent.) were still receiving cortisone, in 65 (15 per cent.) cortisone had been stopped because of a remission, in 102 (23 per cent.) cortisone had been stopped because of an untoward effect, and in ten (2 per cent.) for other reasons.

The results in 546 patients followed for 12 months and in 310 patients followed for 36 months are summarized in Tables I and II (overleaf). In these Tables the grade of improvement and functional capacity are shown according to the criteria adopted by the American Rheumatism Association.*

In 159 patients with rheumatoid subcutaneous nodules, the nodules increased in size, number, or both in 21, remained unchanged in 79, decreased in 37, and disappeared in nine. There was no record in thirteen.

In 43 per cent. of patients the daily dose of cortisone after the first 3 months of treatment averaged not more than 50 mg., while in 57 per cent. it averaged more than 50 mg. As would be expected, there were many more remissions in the patients who required smaller doses than among those who required larger doses. Conversely, undesired effects occurred somewhat more frequently in those receiving the larger doses.

One or more undesired effects which were considered to be of major significance (psychosis, peptic ulcer, fluid retention, pathological fracture, glycosuria, thrombosis, infection or masking of infection) occurred in 46 per cent. of the patients. Minor undesired effects (moonface, acne, hirsutism, striae, emotional instability, redistribution of fat, menstrual irregularity, excess fatigability)

* Steinbrocker and others (1949). *J. Amer. med. Ass.*, **140**, 659.

TABLE I
546 PATIENTS OBSERVED FOR A PERIOD OF 12 MONTHS

Months since Start of Cortisone	Progress of 408 Patients on Cortisone for 12 Months										Disposition of 138 Patients on Cortisone for less than 12 Months				
	Grade of Response					Functional Class					Reasons for Stopping Cortisone				Left Study or Died while on Cortisone
	I	II	III	IV	N.R.	I	II	III	IV	N.R.	Remission	Insufficient Benefit or Worse	Toxicity	Other	
0	—	—	—	—	—	23	133	209	51	2	—	—	—	—	—
6	15	167	179	38	9	50	217	113	20	8	16	31	25	1	2
9	22	157	181	40	8	59	222	101	20	6	33	37	33	2	4
12	22	151	191	39	5	59	216	114	16	3	43	47	41	3	4

TABLE II
310 PATIENTS OBSERVED FOR A PERIOD OF 36 MONTHS

Months since Start of Cortisone	Progress of 26 Patients on Cortisone for 36 Months										Disposition of 284 Patients on Cortisone for less than 36 Months				
	Grade of Response					Functional Class					Reasons for Stopping Cortisone				Left Study or Died while on Cortisone
	I	II	III	IV	N.R.	I	II	III	IV	N.R.	Remission	Insufficient Benefit or Worse	Toxicity	Other	
0	—	—	—	—	—	1	5	12	8	—	—	—	—	—	—
6	—	10	14	2	—	2	12	8	4	—	16	31	25	1	2
9	1	7	14	3	1	3	11	8	4	—	33	37	33	2	4
12	1	9	13	2	1	2	12	9	3	—	43	47	41	3	4
24	1	10	13	1	1	4	12	7	2	1	70	85	71	15	16
36	1	9	14	2	—	4	12	8	2	—	77	99	77	15	16

were reported in 72 per cent. of the patients. There appeared to be a greater tendency for pathological fractures and infections to occur in the older patients.

Twenty-nine of the patients died during the course of the study, of whom 23 were over 50 years of age and thirteen were over 60. In 23 (4 per cent.) of the 546 patients, the cause of death was possibly related to cortisone therapy.

Discussion.—DR. LEWIS COZEN (*Los Angeles, Calif.*): I did not understand the percentage of major toxic effects in the entire group. I should like to ask Dr. McEwen to elucidate that.

DR. MCEWEN: In the total group of 546 patients 54 per cent. had no major undesirable effects, or, conversely, 46 per cent. did have them.

DR. RUSSELL L. CECIL (*New York, N.Y.*): Dr. McEwen, I wonder if you had the same reaction we had on analysing our figures. When we got down to statistics, we concluded that unfortunate reactions to cortisone therapy were not too frequent. We found, in other words, that we were doing a better job for our patients with cortisone than we had thought we were doing. I wonder if others have had the same feeling.

I think there is a psychological explanation; when you do get into trouble, when a patient has a severe emotional reaction, or an ulcer starts bleeding, you begin to think, "I don't want to fool with this stuff".

Then you study forty or fifty cases and see some of the good results obtained, and you feel better.

DR. CHARLES M. PLOTZ (*Brooklyn, N.Y.*): Two years ago we presented a comparison between one hundred patients who had been treated with cortisone and a group of patients we had collected with Cushing's syndrome. I think it is interesting to notice that Dr. McEwen's statistics to-day are very similar to those which we had at that time.

I should like to ask Dr. McEwen why he includes glycosuria as a major undesirable side effect, and, also, how he explains the fact that, while the total incidence of side-reactions is approximately the same in the older age group as in the other patients, the incidence of infection seems considerably higher in the older patients.

Of course the incidence of pathological fracture is higher among the older patients because of the normal incidence of osteoporosis in older people.

DR. J. ALBERT KEY (*St. Louis, Mo.*): Has there been any attempt to determine whether or not this therapy has influenced the natural course of the disease.

DR. DAVID H. KLING (*Los Angeles, Calif.*): Was cortisone the only treatment, especially in the cases which received the smaller dosage, or were salicylates or other adjuvants given?

DR. MCEWEN: It is always disconcerting, to see how statistical analyses of large numbers of patients can upset one's ideas regarding therapeutic effects.

For example, I should have sworn that the subcutaneous nodule of rheumatoid arthritis melts away under cortisone; I certainly gained that impression from seeing what has happened in a few patients. But here,

in the analysis of a large number of nodules, we find many that were not affected.

In answer to Dr. Plotz, I have no good reason why glycosuria was included as a major side-effect. I think he is implying that we should not worry too much about it, and with that idea I agree entirely. I would rather not try to explain the question of infections in the older patients until the data have been more carefully appraised by statistical standards; it may well be that the differences are not statistically valid.

So far as Dr. Key's question is concerned, Dr. Bunim is to present a paper immediately after this report in which an attempt is made to draw conclusions regarding the natural course of the disease. I think his data will answer Dr. Key's question better than mine.

In answer to Dr. Kling, may I say that we have data on the point he has raised. For instance, as I remember it, 71 per cent. of the patients receiving cortisone also received salicylate. We have data on the clinic physician's opinion as to the usefulness of various forms of concomitant therapy, but so far we have not fully analysed them.

A Comparison of Cortisone Acetate and Aspirin in the Treatment of Early Cases of Rheumatoid Arthritis. By H. F. WEST,* *Sheffield, England* (by invitation).

At the 1953 meeting in New York, Prof. A. Bradford Hill and Prof. J. H. Kellgren described in detail the nature of the strictly controlled cortisone acetate and aspirin trial in the treatment of early cases of rheumatoid arthritis which had been organized by a committee of the Medical Research Council and Nuffield Foundation. In this study 61 patients in the early stages of rheumatoid arthritis were allocated at random to treatment with either cortisone acetate (30 cases) or aspirin (31 cases). Two comparable groups of these cases were thus assembled and they have now been treated and observed for one year. For most of the year treatment was "individualized" by the physician-in-charge of each patient at a level sufficient to restore maximal functional efficiency without producing serious side-effects.

Observations made one week, 8 weeks, 13 weeks, and approximately one year after the start of treatment reveal that the two groups have run a closely parallel course in nearly all the recorded characteristics, viz. joint tenderness, range of movement of wrist, strength of grip, tests of dexterity of hand and foot, and clinical judgments of the activity of the disease, of the progress of the patients, and of their functional capacity. The haemoglobin level and blood sedimentation rate were slightly more favourably influenced by cortisone acetate, but in no other respect do the two groups differ materially.

In each group the disease was judged at the end of one year to be slightly active or inactive in about three-quarters of the patients, and in each group some two-fifths of the patients were regarded as capable of normal work and activity. For practical purposes, therefore, there appears to have been surprisingly little to choose between cortisone and aspirin in the management of these early cases of rheumatoid arthritis.

* Dr. West spoke as a representative of the Joint Committee of the British Medical Research Council and Nuffield Foundation which organized the Cortisone-Aspirin Trial.

Discussion.—DR. CURRIER MCEWEN (*New York, N.Y.*): At the time the evaluations were made was therapy continued or did you stop therapy temporarily?

DR. WILLIAM H. GOODSON, JR. (*Kansas City, Mo.*): Did the patients on cortisone have thyroid or any other endocrine preparation?

DR. EPHRAIM P. ENGLEMAN (*San Francisco, Calif.*): First, do we have any information regarding the severity of the disease in these two groups? Secondly, did the examiner know what drug was being used?

Most of the criteria used here are subjective, with the exception of the haemoglobin and sedimentation rate, and, specifically, no information is given regarding the effect upon effusion.

DR. RUSSELL L. CECIL (*New York, N.Y.*): Were there any toxic effects in the adults on aspirin?

DR. DAVID H. KLING (*Los Angeles, Calif.*): What was the dosage of cortisone and was it a constant dose or was it on a decreasing scale? What was the dose of salicylate? Evidently it took cortisone to make us realize how good a drug aspirin is.

DR. LEWIS COZEN (*Los Angeles, Calif.*): Was the total series large enough to be significant, statistically?

DR. J. ALBERT KEY (*St. Louis, Mo.*): Was any cognizance taken as to how these patients felt? I think that is a very important asset on the side of cortisone. It seems to me that if you give patients cortisone they feel a lot better. After all, that is what they come to the doctor for.

DR. JOHN LANSBURY (*Philadelphia, Pa.*): Were there any side-effects from cortisone?

DR. CHARLES M. PLOTZ (*New York, N.Y.*): I think, in connexion with what Dr. Key said, I should like to know how the dose of cortisone was regulated in these patients. Was it regulated to keep them at the same level of subjective or objective improvement as aspirin would give, or was the dose of cortisone given for maximum improvement?

DR. WEST: We made observations quite frequently throughout this trial; those recorded on the chart were taken when the patients were having their maintenance dose. They were not taken when the patients were off treatment except in those few who were considered not to need further treatment.

In answer to the question whether they were given any thyroid in addition to cortisone, none of them were given thyroid or other endocrine therapy.

Do we have any data as to severity? I think the best data regarding severity is the sedimentation rate and the scatter of sedimentation rates. The average was 42 mm./hr (Wintrobe) for both groups when treatment was begun.

Toxic effects? An equal number of side-effects was seen with both cortisone and aspirin. None of these was severe, and in no case was treatment stopped because of them. In some cases it was reduced slightly. There were no fatalities or serious side-effects at all.

Dosage of cortisone? The cortisone was given on a 3-monthly plan. At the beginning of the 3 months they started with the originally suggested schedule of high dosage, dropping down after 4 or 5 days to 100 mg., and that was kept on for a week. The dose was then dropped to 50 mg. for one week. After that, for the rest of the 3 months, the physician would give as much as was considered necessary short of causing severe side-effects.

At the end of 3 months, treatment was stopped for one week, and a record was made during that one week, which is not included in the chart.

Was the series large enough? I think the statisticians thought the series was large enough.

What about the feelings of the patients? In the early weeks of treatment the cortisone patients knew they were on cortisone, but towards the end of the year they disputed which tablet was which, indicating that the feelings of well-being had evaporated somewhat.

Results of Prolonged Cortisone Administration in Rheumatoid Arthritis—A Four-Year Study. By JOSEPH J. BUNIM, *Bethesda, Md.*, and MORRIS ZIFF and CURRIER MCEWEN, *New York, N.Y.*

The purpose of this report is to present the data collected from observation over a 4-year period of 78 patients with rheumatoid arthritis (including nine cases of juvenile rheumatoid arthritis) who were treated with cortisone for intervals varying from a few weeks to almost 4 years. The patients were examined every 4 weeks, or more often, during the study. At the end of the period 44 per cent. of the patients who had remained under observation were still receiving cortisone daily. The results have been analysed to yield information concerning the following:

Composition of the group according to certain clinical features of rheumatoid arthritis;
Age and sex distribution;
Duration and stage of arthritis;
Duration of cortisone therapy;
Average daily maintenance dose;
Results in functional improvement as measured by four different criteria;
Relation of duration of therapy to grade of therapeutic response;
Comparison of certain factors in the groups that exhibited Grade I and Grade III or IV response;
Behaviour of subcutaneous nodules during therapy;
Appearance or extension of bone destruction despite maintenance therapy and good clinical response;
Undesirable effects, peptic ulcers, fractures, and one death from overwhelming sepsis.

Discussion.—DR. ARTHUR W. BAGNALL (*Vancouver, B.C., Canada*): I wonder whether remission was achieved while still on the drug or after it was stopped. What was the period of time involved?

DR. H. F. WEST (*Sheffield, England*): I should like to ask whether Dr. Bunim saw in any patient with rheumatoid arthritis a marked improvement in the radiological appearance of any joint during the course of one year. I ask because I have not seen this occur, but I have seen a patient with ankylosing spondylitis, with hand involvement, improve remarkably radiologically on high ACTH therapy.

DR. PHILIP S. HENCH (*Rochester, Minn.*): This is a thought-provoking paper. There is more to it than meets the eye. Some of Dr. Bunim's patients under cortisone therapy have presented an interesting clinical dissociation: even though they are subjectively and objectively better, certain laboratory data suggest progression of the disease, *e.g.* a "roentgenographic worsening". All of us have seen such clinical dissociations in patients who have developed either a spontaneous clinical remission or a therapeutic one induced by older remedies. I have often seen a rheumatoid spondylitic develop what seems to be a complete clinical remission which continued for several years; but as time went on, despite the continued remission, the changes in the spinal roentgenograms became much more advanced.

Whenever I see such a dissociation I ask myself: Which is the best index of the activity of disease, the symptomatic remission or the roentgenographic (or other) "evidence" of progression? Which is the "disease", the disturbed physiology which produces the symptoms or the local pathological change which produces radiological abnormalities? Certainly, as far as the patient is concerned, it is the former. Perhaps the "progressive *x*-ray changes" are manifestations, not of progressively active disease in spinal tissues, but of progressive healing, the increasing syndesmophytes representing a specialized form of scar tissue, the slow formation of which continues long after active inflammation has subsided.

During the last 6 years we have all run into certain difficulties related chiefly to semantics. First, the results of the cortisones were so unlike that of older remedies that we had to establish new criteria to indicate the speed and degree of relief. I note that our Association now has a new committee to bring our therapeutic criteria up to date.

In evaluating the significance of a dissociation such as we are now discussing, we must ask ourselves: Is the patient worse or is the "chart" worse? I think it is quite possible for a patient to be truly better and his disease really less active, although some one biological alteration may appear worse. Rheumatoid arthritis presents many such dissociations: marked clinical improvement with tardy normalization of serum globulin, sedimentation rate, etc.

This leads to the question: "Just what is the disease known as rheumatoid arthritis and where is its main headquarters?" Sometimes it is chiefly a disease of joints, but often the systemic manifestations are more disturbing than the articular. Which organ is the site of this major disturbance, the primary pathological physiology? Which organ controls the fate of the rheumatoid joint? Is it the liver, the adrenals, the synovia? After 30 years in rheumatology, I must confess I do not know.

DR. BUNIM: I don't think Dr. Hench expects an answer! In reply to the first question on remissions, however, we at first had some doubts about what we should call a remission. A patient on cortisone, having complete relief of all symptoms, a complete suppression, can one say he has remission? We thought back to our friends the haematologists, who talk about the patient with pernicious anaemia who has remission and will continue to have a remission so long as he gets liver extract or B_{12}.

However, this quandary was not as great as we expected. Of the seventeen patients who had remission, only one was continued on the drug. In sixteen patients the drug was discontinued, and not one of them has yet had a relapse, though some have now been off it for 3 years.

In answer to Dr. West's question, we have not yet encountered a single case of marked improvement on *x* ray as a result of, or during, cortisone therapy.

Metabolic Effects of Long-Term Cortisone Therapy. By EVAN CALKINS, DONALD M. MITCHELL, and WALTER BAUER, *Boston, Mass.*

The use of maintenance cortisone in many patients with

rheumatoid arthritis has introduced new physiological problems to medical practice. Although the initial metabolic effects of cortisone have been defined; the extent to which these effects are modified with prolonged therapy is not fully understood.

Two patients with chronic, active, rheumatoid arthritis were therefore studied with electrolyte and nitrogen balances before and immediately after the initiation of maintenance cortisone, and at intervals during a subsequent period of 2 and 4 years, respectively. The effect of alterations in calcium and potassium content of the diet and of testosterone was observed. The pattern of one patient's response to stress was studied on two occasions by determining the metabolic balances, eosinophil counts, and 17-keto- and formaldehydogenic-steroid excretion before and after elective surgical operations, carried out under constant diet and cortisone dosage. These results were compared with the response to sudden increase in and cessation of cortisone and to ACTH administration.

Results show that in these patients, who were initially in negative nitrogen balance, prolonged administration of cortisone was associated with an increased and continued loss of nitrogen and other body constituents. Sudden increase in cortisone and surgery were primarily manifested by sodium retention, rather than by an added acute catabolic response. Although there was apparently no adrenal cortical response to surgery, evidence suggests that there may have been increased "utilization" or altered metabolism of adrenal steroids.

Punch Biopsy of Synovial Membrane in the Diagnosis of Articular Disease. By HOWARD F. POLLEY, WILLIAM H. BICKEL (by invitation), and MALCOLM B. DOCKERTY (by invitation), *Rochester, Minn.*

Punch biopsy of synovial membrane now has been carried out 335 times on 276 patients. Minor improvements in the instrument and in the technique of its use (reported in 1951) have added to the facility of this procedure. Punch biopsy of synovial membrane may now be performed on ambulatory as well as hospitalized patients. Transient symptomatic haemarthrosis has been the only cause of morbidity; this has occurred after only four biopsies (about 1 per cent.).

The knee is at present the most suitable site for punch biopsy of synovial membrane, but in certain instances the ankle, elbow, and shoulder joints have been successfully examined by this procedure. Synovial membrane so obtained has been satisfactorily comparable to that obtained by arthrotomy or other surgical procedures. Trials of a new, smaller instrument, which may be suitable for biopsy of small joints, such as the interphalangeal joints, is now in progress.

Punch biopsy is especially helpful in the diagnosis of monarthritis. Recognition of rheumatoid arthritis, gouty arthritis, articular infections, metaplasia of synovial membrane, and other articular diseases has been accomplished. Punch biopsy also provides the opportunity for additional information in the evaluation of therapy and study of the serial changes in synovial membrane both in various rheumatic diseases and in others in which synovitis may be an associated finding. With this procedure suitable material also may be obtained for tissue culture and chemical studies. As additional experience is accumulated, concepts of the pathogenesis of articular diseases may be clarified.

Discussion.—DR. PHILIP S. HENCH (*Rochester, Minn.*): Perhaps it is not immodest to say that in about 98 per cent. of cases of articular disease an experienced rheumatologist should be able to make a satisfactory clinical diagnosis from the history, physical examination, roentgenograms, and routine laboratory tests. But in about 2 per cent. of our cases we need special techniques such as that described by Dr. Polley.

In India all cows are sacred. In the United States, until recently, the human joint, even when diseased, was a "sacred cow", not to be violated even by the pathologist doing an autopsy on a dead rheumatoid patient! When I was a young rheumatologist at the Mayo Clinic we had a very able and zealous pathologist who prided himself on the high percentage of post mortems obtained and on the completeness of the examinations. When relatives refused to permit him to extend an abdominal (operative) incision made before death he was still able to make an extensive examination, not perhaps extending to the pineal but certainly including the thyroid. And yet so inviolate were the joints in those days that he would examine a diseased one for us only on the rarest occasions, a most frustrating experience for me.

In recent years the situation has improved somewhat as far as joints at *post mortem* are concerned. But incisional biopsies of joints are still performed on rheumatic patients with undue hesitation, and muscle biopsies are done even less often. How little we know about the pathological histology of articular tissue in lupus erythematosus, in psoriasis! And how very fragmentary is our knowledge of diseased muscles! I develop influenza and my muscles ache all over: what type of inflammation is present? What changes characterize the muscles in an "acute wry neck"? And when my *derrière* hurts after a spring horse-back ride, are the symptoms due to some temporary inflammation in the muscles or a non-inflammatory chemical change?

But now we can extend our knowledge of synovial pathology, at least of the knees, without the necessity for incisional biopsies, scars, etc., and Dr. Polley's needle biopsies have been very useful in diagnosis.

DR. J. ALBERT KEY (*St. Louis, Mo.*): I was not too impressed by the title of this paper because it called to mind immediately a paper by Mark Sherman, which very few people have ever seen, on the non-specific inflammatory changes in synovial tissue. Often we have trouble making diagnoses after surgical biopsy.

In a biopsy of tumours, a good deal depends upon where you take the tissue, and the same is true in biopsy of synovial membrane.

However, after having seen Dr. Polley's slides and his ingenious instrument, my opinion has changed.

DR. CURRIER MCEWEN (*New York, N.Y.*): We have been rather discouraged with the results we have obtained to date with this technique, because of the frequency with which competent pathologists have made a histological diagnosis merely of non-specific synovitis. You encourage me to tackle the problem again.

DR. POLLEY: The generous and thoughtful comments of our orthopaedic friends, such as Dr. Key, are very welcome. It seems to me that the essence of the remarks of

Dr. Key and also of Dr. McEwen is that we still have much to learn about synovial pathology.

In addition to the pathologist's report, it has been helpful to us as clinicians to study the tissue obtained by punch biopsy of the synovia in attempts to correlate both clinical and pathological findings. We like to think that in this way we may accentuate the interests of pathologists in rheumatic diseases and thereby further benefit ourselves as clinicians.

Like other technical procedures, facility with the punch biopsy of synovia is improved by experience. However, the technique is not a difficult one; it may be helpful to use this procedure initially on the thick boggy synovia found in some rheumatoid joints. Initial use of general anaesthesia also may help instill confidence in an ability to perform the procedure and thereby facilitate improvement of the technique.

My colleagues and I hope that many of you will be as intrigued as we are by the potentialities of further investigation with punch biopsy of synovia. Your interest and efforts may result in further understanding of many little understood aspects of rheumatology.

Local Anti-Rheumatic Effectiveness of Higher Esters and Analogues of Hydrocortisone. By J. L. HOLLANDER, E. M. BROWN, R. A. JESSAR, N. SMUKLER, L. UDELL, and M. A. BOWIE, *Philadelphia, Pa.**

Intra-articular hydrocortisone acetate therapy has been limited in usefulness for some arthritic patients because the beneficial effect was too transitory. Our previous studies have shown that the injected hormone is absorbed and retained by the synovial lining of the joint without splitting the ester. Because less soluble analogues or esters of hydrocortisone might thus have a longer effect, certain compounds were given intensive clinical trials.

Hydrocortisone t-butyl acetate was injected into the rheumatoid or osteo-arthritic joints of more than 100 patients who had previously experienced only minimal or transitory local relief after the same dose of hydrocortisone acetate. The patients were not informed of the substitution. In approximately two-thirds of the cases the degree of subjective and objective improvement was appreciably increased, and the duration of effectiveness multiplied from *two to ten times*. In most of the remaining one-third no difference was noted, but in a few the effectiveness appeared less.

Allo-dihydro-hydrocortisone was similarly assayed in twelve cases, but was found completely ineffective in all. Another analogue, *9-alpha-chloro hydrocortisone*, was slightly more effective than hydrocortisone acetate in seventeen cases. Comparative results from *hydrocortisone caprylate* and *hydrocortisone benzoate*, assayed as above, were also obtained.

The results so far indicate that the use of certain less soluble esters of hydrocortisone may increase the practicability of intra-articular hydrocortisone therapy.

Discussion.—DR. IVAN F. DUFF (*Ann Arbor, Mich.*): We have compared the effectiveness of intra-articular hydrocortisone acetate, hydrocortisone t-butyl acetate and a free alcohol of hydrocortisone; the steroid dosage varied from 37·5 to 50 mg. Our results confirm those described by Dr. Hollander. Approximately 50 per cent. of a comparable group of patients with active rheumatoid arthritis receiving the hydrocortisone acetate or hydrocortisone (free alcohol) obtained clinical benefit lasting from 4 to 10 days. By way of contrast, 50 per cent. of those receiving injections of hydrocortisone t-butyl acetate reported symptomatic relief lasting from 11 to 20 days.

DR. RICHARD H. FREYBERG (*New York, N.Y.*): At the suggestion of Dr. Hollander and through the kind co-operation of Dr. Alpert, our research group has had an opportunity of observing the effect of the intra-articular injection of hydrocortisone t-butyl acetate, compared with the effect in patients who had also received hydrocortisone acetate suspension intra-articularly.

Our series is rather small, only eighteen patients, all with rheumatoid arthritis, of whom sixteen had injections into the knees, and the other two into the hips—an average of three injections of t-butyl acetate in each case.

Our results in regard to duration of improvement, time of initial onset of improvement, and degree of improvement, are as follows:

Duration.—Eleven of the eighteen patients (61 per cent.) had the same length of benefit with t-butyl acetate as they had with hydrocortisone acetate suspension.

In seven patients (39 per cent.) there was a significant increase in the duration of benefit, but in no instance did it exceed 200 per cent. of that produced by hydrocortisone acetate. The results were quite consistent, with repeated injections in the same patient.

Speed of Effect.—Initial benefit was a little slower with the t-butyl acetate preparation. Sometimes there was a 12 to 24 hr delay in response.

Degree of Benefit.—In eleven of the eighteen patients (61 per cent.) we considered the degree of benefit to be the same. In seven (39 per cent.) there was a slight to moderate increase in the degree of relief obtained.

Our observations agree quite well with Dr. Hollander's. There is about a 40 per cent. chance of obtaining a moderately increased degree of benefit, and about the same chance of a significantly prolonged benefit from hydrocortisone t-butyl acetate as compared with hydrocortisone acetate. In a few of the patients in whom there was no benefit from injections of hydrocortisone acetate, moderately good results followed the injection of t-butyl hydrocortisone acetate.

DR. HOLLANDER: I think that the results presented by the other groups, all things considered, are quite in agreement. We always expect the fellow who reports it first to be the most optimistic. Our series was larger, and it is very easy, in smaller groups, to get a stretch of patients who are not very good responders.

In our own group, each of us took a series of our own cases and did not total them up until the end. It was surprising the variation percentage-wise in degree of improvement and duration of improvement among our own group, before we lumped them all together. One of us had only 40 per cent. of the patients receiving considerable superiority from the hydrocortisone t-butyl acetate, and others of us obtained as high as 70 per cent.

I think if we say 40 to 50 per cent. do definitely achieve better results from hydrocortisone t-butyl acetate as compared with the acetate, we are probably safe. We are *still* looking for something that acts longer and better.

Suppressive, as compared with Analgesic Hormonal Therapy, in Patients with Rheumatoid Arthritis.* By LAURANCE W. KINSELL, *Oakland, Calif.*

One may elect to use one of at least four possible

* See also p. 297 of this issue.

* See also p. 307 of this issue.

procedures in the application of hormonal therapy to patients with rheumatoid arthritis:

1. Complete avoidance of such therapy.

2. A relaxed approach, in which the patient is instructed "to take two, three, or four tablets of cortisone if his joints hurt".

3. Carefully controlled administration of ACTH-cortisone in conjunction with salicylates, the objective being minimal hormonal dosage compatible with reasonable activity and comfort.

4. Intensive initial hormonal therapy under precise hospital control, the objective being the production of a complete quiescence of inflammation within one week, as evidenced by disappearance of pain, swelling, and normalization of the sedimentation rate, and maintenance of the remission with minimal effective dosage.

All responsible physicians who treat patients with arthritis will agree that the second course is to be avoided under any circumstances. Agreement stops here.

The fourth procedure has been used by us in more than forty patients with rheumatoid arthritis, in the course of the past 4 years or so. Initial therapy consists of intravenous ACTH, usually in conjunction with oral cortisone or hydrocortisone. When the sedimentation rate has become normal, the dosage is gradually tapered and the patient is usually discharged from the hospital at the end of 2 weeks, on maintenance dosage. In the months which follow, the dosage is further reduced as the patient's progress permits. The net results of such therapy are better than those obtained with the third or "super-aspirin technique" noted above. If such suppressive therapy is to be used, a precise programme must be followed, including particularly the use of diets designed to minimize the untoward effects of long-term hormonal therapy.

Discussion.—DR. MORRIS ZIFF (*New York, N.Y.*): I should like to know in what percentage of his patients Dr. Kinsell has been able to bring the sedimentation rate to normal. This, in our experience, has been a difficult thing to accomplish.

DR. WILLIAM H. GOODSON, JR. (*Kansas City, Mo.*): In what form does Dr. Kinsell give protein and how does he get his patients to take that much?

DR. CHARLES RAGAN (*New York, N.Y.*): How many patients had gastro-intestinal intolerance?

DR. H. F. WEST (*Sheffield, England*): Has anyone else found extra wide variations in sedimentation rate when the proportion of protein was changed, or when the diet was changed to fats with no carbohydrate?

DR. EDWARD F. ROSENBERG (*Chicago, Ill.*): Why did Dr. Kinsell have almost 16 per cent. incidence of psychosis?

DR. THEODORE B. BAYLES (*Boston, Mass.*): Do I understand that Dr. Kinsell is giving ACTH and cortisone concomitantly?

DR. KINSELL: The form of protein in the diet presents a difficult problem from the anaesthetic standpoint. It is not easy to give a diet of 100 to 150 g. protein and still have a low sodium intake.

We have two general types of diet. In one of them we use synthetic protein supplements (that is, either desalted milk or desalted skimmed milk), and large amounts of washed cottage cheese. In the other, very large amounts of nuts are used because they are low in sodium and high in protein of excellent biological value.

We have five standard diets ranging from 1,400 to 3,000 calories. The patient receives adequate indoctrinations in diet while he is in the hospital.

The high incidence of both gastro-intestinal intolerance and psychosis is unquestionably due to the large dosage in many patients. It is in such patients that we have had to "back out". We know that a certain proportion of patients will be unable to continue with the high dosage necessary for complete suppression.

Regarding diet and 17-ketosteroids, as far as I know, no one else has administered formula diets with this amount of fats and no carbohydrate. No mixed diet contains this vast amount of fat, high protein, and no carbohydrate. We used Lilly's enteric-coated 1-g. tablets of potassium chloride.

The key to the problem of reducing the E.S.R. to normal is continuous intravenous ACTH with as much as 600 to 800 mg. cortisone daily in addition.

We either get the E.S.R. down to normal or we discontinue therapy because the patient manifests one of two major complications (psychosis or gastro-intestinal trouble). The E.S.R. was, in fact, brought down to normal in 37 patients in our series of forty.

For long-term maintenance, any patient that requires more than 50 mg. cortisone daily is given both ACTH and cortisone. For patients who are maintained on less, we usually give cortisone alone, for the reason that it can be given orally. We are worried about adrenal atrophy.

In patients whose ACTH response curves are subnormal, even less than 50 mg. daily, we give both.

Natural History of Haemolytic Streptococcal Infection in Childhood. By LOWELL A. RANTZ, *San Francisco, Calif.*

A 4-year study has defined the natural history of haemolytic streptococcal disease in childhood. Infection and re-infection by these organisms during the first 4 years of life was a commonplace. During this period the clinical illness was characterized by the lack of an acute onset, by low-grade or absent fever, by rhinorrhoea, by a protracted unself-limiting course, and by the occurrence of frequent suppurative complications. Antibody production was feeble.

After the fourth year the disease pattern changed so that progressively more of the infections were associated with an acute febrile onset, sore throat, exudative tonsillitis and pharyngitis, skin rash, and a vigorous antibody response.

Rheumatic fever and lesser manifestations of the rheumatic state occurred after streptococcal infection in children more than 4 years old, but were never observed in younger children.

Evidence has been obtained which supports but does not establish the validity of the hypothesis that the changing patterns of clinical response to haemolytic streptococci are the result of repeated infection by these organisms with an alteration in tissue response, presumably on an immunological basis.

Discussion.—DR. CURRIER MCEWEN (*New York, N.Y.*): Do you mean that, once having had streptococcal infection, were the children more apt to have other infections, or didn't you say that?

DR. RANTZ: Yes. I am not sure whether these are statistically acceptable values because the group is fairly small, but consistently throughout this investigation we were impressed with the fact that once a child had had haemolytic streptococcal infection he was subject to other infections more often than those who had not had streptococcal disease. They seemed more susceptible, but I do not think we can settle the problem.

DR. CURRIER MCEWEN: One more question that follows naturally from the other. Your streptococci were typed. Can you say whether the new infections were due to other types or might they have been flare-ups due to a carrier-state?

DR. RANTZ: Wherever it was possible to do typing we did so. Unfortunately, in this area, as throughout the United States, many of the civilian strains are untypable. We also had evidence of new antibody responses in practically all cases.

DR. T. DUCKETT JONES (*New York, N.Y.*): Did any of these children have glomerulo-nephritis, and, if so, when did it come on, and were they all Type 12?

DR. RANTZ: None of the children had glomerulo-nephritis, in spite of the fact there were twelve well-defined cases of Type-12 infection. So, I have no information about glomerulo-nephritis in this series, but some years ago we had glomerulo-nephritis appearing in very small children. I have had several cases of glomerulo-nephritis in children under 2 years old, which is different from the pattern of rheumatic fever, or seemed so to me.

PRESIDENT RAGAN: Did two infections with Type 12 take place or was that the same infection over a 2-month period?

DR. RANTZ: It was the same.

DR. JOSEPH J. BUNIM (*Bethesda, Md*): Were suppurative sequelae of haemolytic streptococcal infections in the older children in any way predicated on the antibody response.

DR. RANTZ: I think so, but I can't positively prove it. In other words, I believe that is probably right, and it is probably the changes in immunological response that are responsible for these complications, but, as I said, I do not know how to prove it. Wherever you look you find hints, an association with more intense antibody response in individuals who develop rheumatic fever.

DR. J. A. LICHTY (*Denver, Col.*): Has Dr. Rantz any idea whether any of these children might be going to be rheumatics, from any of the studies. We should so much like to be able to spot these children before they get their first attack.

DR. RANTZ: No, I don't think so.

DR. WILLIAM H. GOODSON, JR. (*Kansas City, Mo.*): I have the impression that Dr. Rantz does not see tonsillitis and otitis media in small children. Out in the neighbourhood where we live, acute pharyngotonsillitis with exudate on the tonsils, and an occasional mastoid infection are very common in children between the ages of 6 and 18 months. The same children, followed over a period of years, may have re-infections, farther and farther apart, until they get to be 6 or more years old, when the re-infections practically disappear.

DR. RANTZ: I thought I brought out that suppurative complications with otitis media were extremely common in such small children. We were unable to satisfy ourselves, though, when we examined the pharynx of such small babies that there was really exudative type tonsillitis of the adult type.

PRESIDENT RAGAN: Can you, from your data, state definitively whether this difference in antibody response after the age of 4 years is due to previous re-infection with streptococci or it is due to ageing?

DR. RANTZ: I can't positively state that.

PRESIDENT RAGAN: Have you any patients that did not have streptococcal infection who had a good antibody response at the age of 4 years?

DR. RANTZ: We did not have a study so defined; we were following many patients into this older age group from infancy.

PRESIDENT RAGAN: In a clinic for healthy babies, couldn't it be determined?

DR. RANTZ: I think you could design something that would determine it, but it was not done in this study.

Functional Status of the Pituitary-Adrenal System in Rheumatic Fever. By VINCENT C. KELLEY, *Salt Lake City, Utah* (by invitation).

The circulating concentrations of 17-hydroxycorticosteroids, the predominant hormones produced by the adrenal cortex, are abnormal in rheumatic fever patients. The concentrations of these steroids observed in patients in various phases of rheumatic fever are related to the duration of illness.

TABLE

CIRCULATING CONCENTRATIONS OF 17-HYDROXY-CORTICOSTEROIDS IN PATIENTS WITH VARIOUS PHASES OF RHEUMATIC FEVER

Group	17-Hydroxycorticosteroids				
	No.	Mean	Standard Error of the Mean (g. per cent.)	Range	*p* (vs controls)
1 Controls ..	40	12·0	±1·29	0–28·7	
2 "Early Acute" R.F... ..	15	23·1	±1·49	14·1–35·2	<0·01
3 "Transitional Phase" R.F.	12	11·8	±2·01	0–30·2	>0·5
4 "Well-established Active" R.F... ..	31	5·9	±0·93	0–16·1	<0·01
5 Inactive R.F.	87	8·3	±0·61	0–19·8	<0·01
6 Chorea ..	27	5·7	±0·86	0–12·8	<0·01

During the first week of rheumatic activity ("early acute") the 17-hydroxycorticosteroids are significantly elevated. During the second week ("transitional phase") the steroid values are extremely variable, whereas after two weeks of rheumatic activity, these values are uniformly low. These values are likewise uniformly low in patients with inactive rheumatic fever and with chorea.

On the other hand, circulating concentrations of endogenous ACTH are normal in the early acute phase but elevated in patients with well-established rheumatic fever, inactive rheumatic fever, and chorea. In these patients the equilibrium state of low 17-hydroxycorticosteroid

and high ACTH concentration is interpreted as indicating adrenal cortical insufficiency. That this adrenal insufficiency is *relative* rather than absolute is indicated by the adequate steroid response of these patients to sufficient ACTH stimulation. In response to an intramuscular dose of 25 I.U. ACTH, rheumatic patients exhibited a mean plasma steroid increase of 26 μg. per cent. as compared with a mean increase of 17·8 μg. per cent. in normal children. That these patients can respond likewise to sufficient *endogenous* ACTH stimulation is illustrated by case examples of steroid levels raised in response to stress.

Hereditary factors may affect rheumatic fever susceptibility. There may be a place for hormone therapy in rheumatic fever.

Discussion.—PRESIDENT RAGAN: Were the patients with the low circulating levels of 17-hydroxycorticosteroids—whom you said were untreated—on salicylate?

DR. CHARLES L. STEINBERG (*Rochester, Minn.*): Do you consider a hydrocortisone response as a non-specific reaction to stress, and have you studied this effect in other infectious diseases? Was the renal insufficiency produced by this type of infection followed by the level of circulating eosinophils?

DR. THEODORE B. BAYLES (*Boston, Mass.*): What do you mean by "inactive" rheumatic fever. Does a patient who had active rheumatic fever at the age of 10 years, who is now 20 years of age, still have abnormally low steroid levels? I think that should be cleared up.

DR. CURRIER MCEWEN (*New York, N.Y.*): From your data, I should estimate an average dose of cortisone for these children would be about 200 mg. daily. Is that correct?

Secondly, have you any data on the possible levels of ACTH or cortisone in patients with active rheumatoid arthritis, just as a comparison?

DR. PAUL J. BILKA (*Minneapolis, Minn.*): Dr. Dougherty said that they could diagnose adrenal insufficiency by looking at a blood smear and checking the lymphocytes. Did Dr. Kelley find these altered lymphocytes in these patients with low 17-hydroxycorticosteroids? It would be of great help to all of us, if we could diagnose adrenal insufficiency by that simple means.

DR. T. DUCKETT JONES (*New York, N.Y.*): What type of murmur are you talking about; if significant murmurs, were they of the same type in the two groups?

PRESIDENT RAGAN: What did salicylates do to the blood hydroxycorticosteroid level?

DR. KELLEY: In answer to Dr. Ragan's first question, the levels of 17-hydroxycorticosteroids presented were in untreated patients, none of whom had received any high-dose salicylate therapy. They were patients as they arrived at our hospital on referral. Some of them had had an occasional aspirin tablet before they came in, but none had received hormone therapy or high-dose salicylate therapy.

PRESIDENT RAGAN: During the 16 weeks they were not on salicylate?

DR. KELLEY: No. That was the time since the onset of illness. They received no therapy whatever.

In answer to Dr. Bayles: We have defined the patient with "inactive" rheumatic fever as one who has been seen by one of us in the University Department of Paediatrics or the state rheumatic fever clinics during an acute attack of rheumatic fever, who has been for at least 6 months symptom-free, and who on the day of the determination had a normal sedimentation rate and no clinical evidence of activity. Some of these have been inactive for as long as 5 or 6 years. We think the low steroid level persists after a patient has once had rheumatic fever, and we are speculating whether it existed before the attack of rheumatic fever, and whether this might be the factor that made him susceptible. We have a few patients who have never had a diagnosable attack of rheumatic fever, but have developed cardiac murmurs and cardiac enlargement over a period of years, who have the same hormone pattern as is present in rheumatic fever patients with low steroid levels and high ACTH levels.

In answer to Dr. Steinberg: If I interpret your question properly, we think the rise in 17-hydroxycorticosteroid level, which occurs during the first week of rheumatic fever, is a non-specific reaction to "stress", just like the rise which occurs in acute meningitis or other acute, severe disease. The difference is that in the other diseases, after this early phase, the steroid levels return to normal and not to sub-normal levels as in rheumatic patients. We feel that the reason for this may be that the rheumatic patient has had a low "normal" level before the onset of illness. With the "stress" he develops elevated levels, which later return to sub-normal levels. We know this to be the case in a second attack of rheumatic fever. We have followed several patients who had a first attack, were included in our inactive rheumatic fever group, and then had a recurrence. While they were in the inactive stage they had low steroid levels, and during a recurrence they followed the same pattern as that seen in other patients during an acute attack.

In answer to Dr. McEwen: The average dose, according to our schedule, depending upon the size of the patient, is about 2·5 to 3 mg. cortisone per lb. This would amount to an initial dose of about 200 to 300 mg. cortisone daily.

We have about a dozen juvenile rheumatoid arthritics. Their steroid levels are consistently low as in rheumatic fever, but not quite so low as in our small group.

I have no answer to the question whether the lymphocytes are altered. If Dr. Dougherty is here he may like to comment. Not being haematologists, we have not used the lymphocyte response as an indicator of the presence or absence of adrenal insufficiency.

Dr. Jones asked about the murmurs present in these patients. With one exception, all had carditis as a major symptom in their acute attacks of rheumatic fever. Several had diastolic murmurs, several had more than one murmur, and all had at least Grade II systolic murmurs.

In the follow-up study we consider any detectable murmur. At the one-year follow-up the two hormone-treated patients had murmurs, which were only audible in certain positions. When we say "no murmur", it means none of us were able to find any murmur, and several different workers have examined each patient.

As to the severity of illness in the two groups, this was not a "blind control" series, but the more severe cases are treated with hormones, so that distortion of the series is in that direction. Occasional patients who were referred specifically for hormone therapy, or insisted upon having it, were included in the hormone group.

In answer to Dr. Ragan's last question, the effect of salicylates on the blood steroid levels is a very interesting and very long story. Patients with salicylate intoxication

have extremely high levels of circulating steroids, as we have reported. This has been found consistently in every previously normal patient with salicylate intoxication. However, in rheumatic fever patients who are treated with salicylates to the point of intoxication, the steroid levels are not raised, but appear to be below normal.

We have taken a large group of normal volunteer medical students and treated them with salicylates in various dosage schedules, corresponding to the schedules used in rheumatic fever. In these subjects we found no consistent elevation of steroid levels at any particular time after administration. However, we were able to demonstrate a raised steroid level at some time during the following 12 hours which was greater than the normal diurnal variation. I think it is more important that we demonstrate an increased rate of removal of steroids from the circulation after the administration of salicylate. This is attributable to some mechanism other than urinary excretion. We feel it probably indicates an increased rate of utilization, but we have no data to substantiate that interpretation.

If I may mention one more thing—we have recently done some studies in which we inject Compound F alcohol and follow the rate of its disappearance from the blood. In contrast to what we expected, the Compound F disappears about one-half as rapidly from the blood of rheumatics as it does from normal individuals. Secondly, when salicylates are administered 2 hours before the Compound F, we can demonstrate an increased release of steroids from the adrenal cortex, but also an increased rate of disappearance of the steroids from the blood, so that the curve extrapolates to 0 after about 2½ hours as opposed to 5 or 6 hours without salicylates.

Prophylaxis against Group-A Streptococci in Rheumatic Fever Patients by the Use of Single Monthly Injections of N,N' Dibenzylethylenediamine Dipenicillin G (Bicillin). By GENE H. STOLLERMAN, JEROME H. RUSOFF, and ILSE HIRSCHFELD, *Irvington-on-Hudson, New York*.

Single intramuscular injections of 1·2 million units of N,N' Dibenzylethylenediamine Dipenicillin G (Bicillin) were administered for two successive years to a group of 138 out-patients, recently recovered from acute rheumatic fever, and to 270 patients hospitalized at Irvington House in the acute and convalescent stages of the disease.

No recurrences of rheumatic fever were observed in either group. In a comparable series, two of 111 patients who received penicillin orally (200,000 units daily), and five of 79 patients who received sulphadiazine orally (1 g. daily), suffered frank rheumatic recurrences.

Of 2,052 throat cultures made monthly from out-patients receiving Bicillin injections, only three were positive for Group-A streptococci. Of 2,010 determinations of antistreptolysin 0 titres made in the same group, a significant rise in titre was noted only twice. During the spring of 1953, 27 per cent. of a control group of clinic patients were found to have Group-A streptococci in their throats.

Between 50 and 75 per cent. of patients receiving Bicillin, who were tested at various times during the study, were found to have detectable levels of penicillin in their sera as long as 4 weeks after an injection.

Of 35 patients found to be carriers of Group-A streptococci upon admission to the study, 31 were cured of the carrier state by a single intramuscular injection of Bicillin. The remaining four showed bacterial relapse after variable periods but were cured by a second injection.

All patients admitted to the study without clinical evidence of heart disease remained normal during the 2-year period of prophylaxis. New valvular lesions did not develop in patients who had organic heart disease initially. Two patients in this group had progressive change in murmurs in the absence of intercurrent streptococcal infection.

4,073 injections were administered to 408 patients during the study. One patient developed urticaria, which subsided within 4 days, and treatment had to be permanently discontinued in one patient. Although local pain, tenderness, and induration, usually lasting 24 to 48 hours, were common, no patient developed an abscess or other serious reaction at the injection site.

Discussion.—DR. JONES (*Columbus, Ohio*): Did the patients develop any other type of infection, and was there a normal response to penicillin therapy?

DR. JOSEPH J. BUNIM (*Bethesda, Md*): In view of the type of follow-up carried out in these cases, is it possible that some might have developed some transitory allergic reaction which escaped detection?

DR. T. DUCKETT JONES (*New York, N.Y.*): In the new statement the American Council on Rheumatic Fever is contemplating putting out, the committee, for the time being, favours parenteral as opposed to oral penicillin. This has resulted in a surprising antagonism from paediatricians.

We have as yet no data about the sensitivities in adults, and I should like to ask Dr. Stollerman if he has any ideas about this, and whether any patients developed L.E. cells.

Also, did the three patients who had a progression of heart disease—this is a relatively small group—have continuous rheumatic fever, or does he infer that, even on the long-acting penicillin prophylaxis, there were subclinical recurrences in a very few.

In the regressions with decrease in heart disease and those with the disappearance of rheumatic heart disease, his percentages are almost identical with those reported by Dr. Bland and reported over a long period of years as regressing in a natural way without prophylaxis.

DR. CURRIER MCEWEN (*New York, N.Y.*): I have been disconcerted to find that some medical men have the impression that because penicillin is long-acting when given intramuscularly, it also has some special virtue, in this regard, when given orally. Of course, the long-acting effect is obtained only when the repository penicillin is given intramuscularly.

DR. JOSEPH EDWARD WARREN (*Pittsburgh, Pa*): Dr. Stollerman has given us a comparison of recurrence rates when one uses sulpha drugs or oral penicillin, and I believe it is unfair to the only competitive regime which is oral penicillin. For comparison we need some data on the relative toxicity of oral penicillin. Many more patients must be studied before we can distinguish between a recurrence rate of only two patients in 130, and none in his group.

DR. STOLLERMAN: In answer to Dr. Bunim: we included

269 hospitalized patients in this series, in addition to the 145 out-patients, for the express purpose of observing them closely daily for any type of allergic manifestation. The incidence of reactions was no different in the in-patients and in the out-patients.

In addition, we performed skin tests at the end of 6 months of Bicillin therapy on 100 patients to see whether they had acquired skin sensitivity to this compound. None were positive. We recognize the limited value of skin testing in detecting penicillin hypersensitivity.

With regard to the question of other infections, I think it is important to mention that there were two patients who developed subacute bacterial endocarditis during this period of prophylaxis. In both instances the organism was found to be sensitive to penicillin and both patients were cured promptly by the usual 4-week course of large parenteral doses of penicillin.

Other unrelated infections included two mild cases of staphylococcal otitis media and pharyngitis, which were cleared up by a course of procaine penicillin G.

In answer to Dr. Jones: I think the antagonism to parenteral penicillin results from the traumatic experience of many doctors who have observed serum sickness in patients receiving injections of penicillin.

I should like to emphasize that we are not trying to pit one form of prophylaxis against another. We are trying to demonstrate a new technique that is available in situations where oral prophylaxis often fails. Such a situation often arises with an out-patient group, where the reliability of oral prophylaxis cannot be guaranteed. We do not introduce this method as a form of prophylaxis to replace completely the administration of penicillin orally. We introduce it as an addition to the practitioner's armamentarium where the risk of recurrence is very great. We think that the risk of penicillin sensitivity when compared to the risk of recurrences in the type of population with which we are dealing is well worth taking. We have little data on the incidence of hypersensitivity in adults who have received Bicillin.

A search for lupus erythematosus-like cells in the blood of fifty patients who had received Bicillin for 6 months was made by one of our staff who was engaged in another study, and no such cells were found.

I cannot at present answer the question whether continuous low-grade rheumatic fever is responsible for the progression of heart disease in the three patients mentioned. I think it will take extensive and prolonged observation to compare this series with the much longer series of Jones and Bland.

In answer to Dr. McEwen, I think carefully controlled studies of the true incidence of penicillin reactions after parenteral as compared with oral administration are sorely needed. It is our impression also that penicillin given orally has a very low incidence of toxicity; we are not sure whether the reaction rates after parenteral administration are a little bit higher.

Finally, I agree entirely with Dr. Warren that this data by no means provides an adequate comparison of parenteral versus oral prophylaxis. We now have a large-scale controlled study under way, which will yield more extensive data on this problem.

Rheumatic Heart Disease in Colorado School Children. By H. J. DODGE and J. A. LICHTY, *Denver, Col.*

A state-wide study of the prevalance of rheumatic heart disease was made in Colorado's 6th grade children. This was prompted by the high mortality rate from this disease in the Rocky Mountain states and its reported high incidence in military posts in this region. The findings of a careful clinical examination of some 11,000 unselected 6th graders* revealed only 74 (0·66 per cent.) cases of definite rheumatic heart disease. For half of these cases there was no diagnosis or history of previous rheumatic fever; 63 additional children were suspected of having some type of heart disease.

Analysis of the data revealed an unusually high prevalence of rheumatic heart disease in the Spanish-American population, in rural areas, and in crowded homes. No association was found with altitude or geographical situation.

Parents of all children with definite or suspected heart disease (all types) received letters recommending further diagnosis and treatment by the family physician. After 2 years, follow-up information was obtained by questionnaires distributed to the families and physicians of 315 such children. Where possible, hospital records were also reviewed. Some information was obtained for 50 per cent. of the children, half of whom were seen at least once by a physician. For children with definite heart disease, the diagnosis had been changed in only 7 per cent. of a group receiving either special diagnostic tests or cardiologist consultation. In contrast, it had changed in 45 per cent. of children not receiving these services. One possible explanation is that family physicians are misinterpreting heart sounds.

The follow-up information revealed that only 14·5 per cent. of children with definite rheumatic heart disease were receiving drug prophylaxis.

Discussion.—DR. JOHN HUBBARD (*Philadelphia, Pa*): Was the subsequent diagnosis and the original diagnosis made by the same individual or the same team, or did it shift, perhaps, from a team to a family physician diagnosis?

Could some idea be given of the type of prophylaxis recommended through this group?

DR. LICHTY: I think the important thing is that the follow-up was done by a family physician. The team has not had a chance to go out to re-study these children.

Most of the children were on sulpha drugs, but I do not believe that we have any preference for any particular prophylactic regime in our state.

Mechanisms involved in the Production of Fibrinoid Necrosis by Endotoxins. By LEWIS THOMAS, *Minneapolis, Minn.*

The basic lesion in the so-called "collagen" diseases is the deposition of fibrinoid material in tissues. The prototype of this group is disseminated lupus erythematosus, in which extensive deposits of fibrinoid occur in the lumen and walls of blood vessels and in surrounding connective tissues. The closest approximation to this histopathological situation obtainable in experimental animals is the generalized Shwartzman reaction, which is produced in rabbits by two intravenous injections of endotoxin from various Gram-negative bacteria. Within a few hours of the second injection, masses of material resembling fibrinoid appear in the glomerular capillaries, resulting in bilateral cortical necrosis of the kidneys.

* Maresh, G. J., Dodge, H. J., and Lichty, J. A. (1952). *J. Amer. med. Ass.*, **149**, 802.

Under certain conditions, similar material appears in the coronary arteries, in association with varying degrees of necrosis of the vessel walls, and it also occurs as vegetations in the mitral and aortic valves.

Serial histological studies of kidneys during the development of the generalized Shwartzman reaction showed that fibrinoid appears within the lumen of glomerular capillaries before there is any evidence of vessel wall damage or necrosis. It is considered probable that the material is derived from the circulating blood. Heparin, which prevents the generalized Shwartzman reaction, also prevents the appearance of fibrinoid in the glomeruli.

Liquoid (Na polyanethol sulphonate), a synthetic polymer, has the property of precipitating fibrinogen from plasma. When injected by vein in combination with endotoxin, it causes a greater than 1,000-fold enhancement of the lethal action of endotoxin, and typical lesions of the generalized Shwartzman reaction occur in all animals. This reaction is completely prevented by prior heparinization.

It is believed that the two stages of the generalized Shwartzman reaction involve the appearance of an abnormal coagulable material in the circulating blood, followed by precipitation of this material within the lumen and the walls of the blood vessels.

Discussion.—DR. EVAN CALKINS (*Boston, Mass.*): Does the heparin go down in the precipitate or is it in the supernate?

DR. MORRIS ZIFF (*New York, N.Y.*): I compliment Dr. Thomas on this excellent paper; I must point out, however, that fibrinoid in different tissues and in different diseases may have an entirely different composition.

DR. C. F. MCLEAN (*Berkeley, Calif.*): Has this anything to do with the so-called fibrinogen B?

DR. MORRIS ZIFF (*New York, N.Y.*): Kellgren, Ball, Astbury, and co-workers, examining the nodules of rheumatoid arthritis, found no evidence of the *x*-ray pattern of fibrin in this type of fibrinoid.

DR. J. ALBERT KEY (*St. Louis, Mo.*): Do you think that this intravascular fibrinoid is the same material as occurs extravascularly around joints and in nodules?

DR. THOMAS: Of the possible differences in fibrinoid in different tissue situations, I think it is possible that fibrinogen might conceivably be precipitated by material giving staining reactions other than polysaccharides, for example, nucleic acid material. There is heparin in the precipitate. It is loosely bound, and easy to get off. It has to be there for the precipitate to go down.

Regarding fibrinogen B, I think there is possibly some relationship between this material and the so-called cold precipitable fraction of semi-purified fibrinogen loss. However, the main difference is, that in our material heparin must be present for full precipitation to occur.

Effect of Hypophysectomy and Growth Hormone on Radioactive Sulphur Uptake in Cartilage. By CHARLES W. DENKO, ALLAN T. KENYON, and DELBERT M. BERGENSTAL, *Chicago, Ill.*

Factors affecting the rate of fixation of radioactive sulphur, S^{35}, into tissues have aroused our interest. Radiosulphur is organically bound into many tissues of normal animals, especially cartilage and other connective tissues. Its incorporation into chondroitin sulphate has been demonstrated.

Young female rats, hypophysectomized and normal, were used in a study to determine the effects of growth hormone on S^{35} fixation. To study the synthetic activity of cartilage repeated injections of S^{35} were given intraperitoneally with and without growth hormone (Armour) daily for 8 days. One day after the last injection, the animals were killed, tissues removed for study, washed, sulphur precipitated as barium sulphate, and radioactivity determined as a measure of S^{35} fixation in the tissues.

Cartilage, especially the xiphoid, costal, and tibial articular (as the tibial cap), was found to contain higher concentrations of S^{35} than the other tissues studied. Hypophysectomy decreased the rate of fixation of sulphur in these tissues approximately 25 to 80 per cent. below that found in normal animals. Growth hormone administered to hypophysectomized rats caused a vigorous stimulation of sulphur uptake, increasing about four-fold in the costal cartilage.

Normal animals receiving similar injections of growth hormone showed a decrease in the fixation of S^{35} by tissues, ranging to 25 per cent. below normal levels.

Thyrotrophin was present as a contaminant in small amounts in the growth hormone preparation used. However, tests of its effects at this contaminating level demonstrated no comparable or appreciable effect on S^{35} fixation in cartilage.

Discussion.—DR. J. ALBERT KEY (*St. Louis, Mo.*): Is there any evidence that there is any increased growth at the rib cartilage as evidenced by deformity of the chest in these animals?

DR. MORRIS ZIFF (*New York, N.Y.*): What is the half-life of the incorporated sulphate in the resting animal and in the hormone-treated animal?

These experiments seem to show that mucopolysaccharides, unlike the collagen of connective tissue, do turn over in the adult animal.

DR. CHARLES L. STEINBERG (*Rochester, N.Y.*): This is a very interesting paper, particularly the emphasis on the effect of hypophysectomy on joints. Hypophysectomy results in splenic atrophy in certain animal experiments. We are familiar with the fact that splenomegaly occurs in some types of rheumatoid arthritis (Felty's syndrome); and it is known in animal work that splenectomy results in hypertrophy of the anterior lobe of the pituitary. This has been offered as an explanation of why splenectomy sometimes gives benefit in rheumatoid arthritis.

Was there any change in the spleen, or atrophy, as a result of hypophysectomy, and was there any change in the uptake of radioactive sulphur in these cases?

DR. DENKO: In answer to Dr. Ziff, we are doing studies on the difference in half-life of incorporated $sulphur^{35}$ in treated and untreated animals, at the present time. In the preliminary state, at 2-week levels, that is in animals killed 2 weeks after the last dose, there appears to be no difference in the slope of the disintegration of the radioactive chondroitin sulphate.

We are continuing this study and have evidence that makes us feel that, in the early stages of disintegration it may not be enough to be detectable. But, in view of

the long half-life of the incorporated material, we have carried on studies lasting up to 2 months. We must carry them on much longer than 2 weeks before we can give you a reliable answer to that question.

DR. MORRIS ZIFF (*New York, N.Y.*): Is all new formation, formation of new growth?

DR. DENKO: No. We have other data that indicate that not all new growth in a hypophysectomized animal at the age of 26 days has the same rate of sulphur fixation. Hypophysectomized animals at the age of 46 days, that is approximately 24 days after the hypophysis has been removed, have approximately the same fixation as rats aged 26 days receiving sulphur initially 4 days after hypophysectomy. There is no appreciable increase in the size of the animal, and there is no effect of growth hormone, or of any endocrine factor, as far as we can determine.

Consequently, we feel there may be a basic process such as trans-sulphation or trans-sulphation which occurs in living cartilage, without the influence of endocrine factors.

As to the evidence of increased growth of the rib cage by deformity of the rib cage, we do know there is some change in the character of the cartilage. In the hypophysectomized animals receiving growth hormone the costal cartilage becomes brittle and changes colour. It becomes more opaque and does not glisten as much, as if an ageing process had gone on.

Furthermore, in these animals there is a noticeable increase in the amount of bony spurring to be detected in a tibial cap.

With regard to the change in the spleen as a result of hypophysectomy, the spleen tissue is so inactive that sulphur uptake or sulphur fixation in the spleen cannot be utilized suitably for this study. However, we have noted a regression of many of the endocrine organs in the hypophysectomized animals. As far as the spleen is concerned directly, it looks the same, but the sulphur fixation cannot be reliably determined.

Size and Shape of Hyaluronic Acid. By B. BLUMBERG, G. OSTER, and K. MEYER, *New York, N.Y.*

A study of the physical nature, *i.e.* size, shape, deformability, etc., of hyaluronic acid, an important constituent of the ground substances of connective tissue, might help in our understanding of the nature of the changes observed during varying conditions of health and disease.

The scattering of light by large molecules provides a method for studying the size, shape, molecular weight, and interaction of the particles. From these studies, the molecule of hyaluronic acid of umbilical cord (analytically protein-free) is found to be a particle of molecular weight about 8 million whose envelope is a sphere of diameter 2,000 Å (similar to that reported by Ogston and Stanier using different physico-chemical techniques for a hyaluronic acid-protein complex containing 30 per cent. protein obtained from synovial fluid). The linear polysaccharide molecule is coiled in some fashion in this envelope and is surrounded by a large volume of water. Indeed, the anhydrous material represents only about 0·25 per cent. of the weight.

Ultracentrifuge studies give a sedimentation constant low for a particle of this size, suggesting that the particle is free draining, *i.e.* that the water can easily circulate through the mesh of linear hyaluronic acid. The diameter of the mesh "fibres" approximates to 10 Å.

The molecule shows flow birefringence, indicating that it is deformable in a sheer gradient, as is to be expected in such a swollen particle.

These observations are related to clinical findings, the gel-sol properties involved, and ion and water binding.

Inhibition of Cortisone Effect on Inflammation and Repair by Cartilage Extracts. By JOHN R. MARTIN, RAFFEAL LATTES, and CHARLES RAGAN, *New York, N.Y.*

Previous communications from this department have shown that the inhibitory effect of cortisone on repair can be overcome by local infection. Recently cartilage extracts have been shown to have a similar effect.

Experimental Studies: The technique of gauze implantation and the cortisone schedule have been outlined previously. In the present work, the effect of cartilage upon the modification of the repair processes by cortisone was studied. Two suspensions were used, one containing powdered autoclaved beef tracheal cartilage, and the other fresh homogenized pig's knuckle cartilage. One group of animals received daily injections of the autoclaved suspension similarly. Daily injections of antibiotics were given. The remaining two groups were controls, receiving injections of the suspending vehicle instead of cortisone. At the end of 5 days, the animals were killed.

Results: Autoclaved Cartilage: The pledgets were partially adherent to the surrounding tissues in the cortisone-treated and control animals. The microscopic picture was identical in both, showing abundant granulation tissue.

Pig's Knuckle Cartilage: The pledgets were partially adherent in the cortisone-treated animals and more so in the controls. The microscopic picture showed a moderate reparative process around the pledget in the cortisone-treated animals which was, however, more abundant in the controls.

Bacterial cultures from the pledgets were sterile in 50 per cent. of each group.

Conclusions: Suspensions of cartilage are capable of suppressing the inhibition of repair by cortisone.

An Epidemiologic Look at the Problem of Classification in the Field of Arthritis. By SIDNEY COBB, WILLIAM MERCHANT, and JOSEPH WARREN, *Pittsburgh, Pa.*

Arthritis survey data have usually been unsatisfactory because they have been neither precise nor disease specific. We are now trying to develop a broadly applicable survey method from our studies with a population of 10,000 people in 3,000 families that have been selected at random from the Arsenal Health District of Pittsburgh. A household survey has identified a large number of persons with rheumatic complaints who are now under clinical study.

We find that persons with rheumatic symptoms far outnumber (6 to 1) those individuals fitting a classical disease description. The majority have not consulted

a physician for these symptoms, suggesting that the sample differs from that seen in clinical practice.

A technique of charting signs and symptoms that help us to visualize this classification problem has been devised. Illustrative cases emphasize the difficulty of deciding when an atypical case is too atypical to be included.

There is an urgent need for limiting definitions. The limits must laterally define the boundaries between diseases and vertically the minimum severity at which the diagnosis is acceptable.

Discussion.—DR. CHARLEY J. SMYTH (*Denver, Col.*): This paper is illustrative of the type of information that is long overdue. I am certain that our work in the future in case-finding and evaluating new drugs will have to go back to work of this type. The group are to be congratulated in presenting data of this sort, because we have no guideposts or index of the frequency of the various types of disease. In evaluating therapy we are confronted with the same problem.

DR. RUSSELL L. CECIL (*New York, N.Y.*): When the Committee on Criteria go over this problem, which is so important, they should give a great deal of attention to monarticular joint disease, a condition that, when I was on the consultation staff at the Veterans Hospital, worried me not a little. Generally, a soldier had come back from the Pacific with a monarticular pain, swelling, and sometimes moderate hydrops. There I sat looking at it, with young students around, and the young doctors waiting for me to make a diagnosis. Many a time I have been embarrassed because I did not know how to classify it.

DR. CHARLES RAGAN (*New York, N.Y.*): I, too, think this work is of fundamental importance.

DR. PHILIP S. HENCH (*Rochester, Minn.*): This careful study must surely have been a labour of love. It is very informative and gives us data of practical importance which we have long needed, a clinical summary we can accept with confidence.

Rheumatoid Arthritis with Remissions: A Study of Eighty Patients. By CHARLES L. SHORT, WILLIAM E. REYNOLDS, and WALTER BAUER, *Boston, Mass.*, and JEAN M. BEAUREGARD, *Montreal, Canada.* (Read by Dr. Bauer.)

Detailed information in regard to the course before hospital admission was obtained from 293 patients with rheumatoid arthritis representing consecutive admissions to a medical service, 80, or 27 per cent., experienced one or more remissions, while in the remainder the course was essentially progressive.

The courses followed by each of the 80 patients who experienced remissions have been graphically portrayed. From these graphs, examples of which will be given, a simple classification of the differing course patterns was derived, based on the length of attacks and remissions. In the large majority of patients, attacks were "brief" (of one year's duration or less), with remissions either "brief" or longer than one year. In the remainder, attacks were "long" (over one year), with either "brief" or "long" remissions. While attacks of over one year were thus much less likely to be followed by remissions, instances were recorded of complete remissions after two to five years of active disease. In the whole group with intermittent course, about twice as much time was spent in remission as in exacerbation.

The remissions began throughout the year, with a peak in May, but exacerbations started more frequently in the colder months, a distribution corresponding to the available figures for the season of onset of rheumatoid arthritis. The rheumatoid arthritic is thus more likely to experience either a serious worsening of his disease or the actual onset of his arthritis in the colder than in the warmer half of the year, though it is not to be finally assumed that climatic changes are necessarily responsible.

Discussion.—DR. SIDNEY COBB (*Pittsburgh, Pa*): As an epidemiologist I am not satisfied with the explanation of the seasonal distribution of any disease, infectious or otherwise, except where the seasonal distribution of an anthropoid vector is the controlling factor. I do not think Dr. Short should feel badly for not having found the reason for the seasonal distribution of rheumatoid arthritis. I suspect that his hypothesis about seasonal variation in the host is likely to prove the most productive.

DR. RUSSELL L. CECIL (*New York, N.Y.*): What every rheumatologist would like would be what one could call an *ad infinitum* remission. Dr. Kammerer pointed out to me a patient with a history of Still's disease, who recovered, and then went for 25 years in remission before developing typical rheumatoid arthritis.

DR. CHARLEY J. SMYTH (*Denver, Col.*): I want to congratulate this speaker, too, because this type of work can only be done by the directors of arthritic clinics.

Such men have a tremendous responsibility in setting some sort of base line for clinical evaluation, so that when problems come from the basic group to the clinic we can make critical, reasonable, and valid deductions as physicians responsible for the care of patients. We have a great educational problem, for many doctors do not know the difference between rheumatoid arthritis and gout, or the variable nature of rheumatoid arthritis itself, and I think the work of this group in Boston is putting a firm basis under some of the loose thinking and fuzzy definitions currently in use.

DR. SHORT: These patients were all carefully screened for gout. One must always think of gout in any form of intermittent arthritis.

I also agree with Dr. Cobb that the seasonal frequency of disease is a subject that might be explored further.

Physico-Chemical Investigation of Synovial Fluid.* By ERNEST FLETCHER, *London, England* (by invitation).

The term viscosity has been used loosely by many workers studying the rheological properties of synovial fluids. Although it is well known that synovial fluid exhibits flow anomalies due to the highly polymerized state of hyaluronic acid, measurements have usually been made in viscometers designed for simple fluids, often no precautions being taken to minimize errors due to its anomalous behaviour. Quantitative studies of this anomalous behaviour have only been made with instruments too complex for routine use.

By using a U-shaped viscometer (described by Scott-

* Most of the experimental work on which this paper is based was done by R. Markham, Esq., B.Sc., Biochemist to the Department of Rheumatism at the Royal Free Hospital, London, and Dr. P. O. Williams, Registrar to the Department.

Blair) with a central horizontal capillary and vertical wide-bore side-arms, a study has been made of viscosity and the anomalies due to stress, capillary radius, and capillary length. This may be used to obtain readings in standard units, and it is possible by this method to compare viscosities directly, unhindered by the modifying effect of the rheumatic disease on synovial fluid.

Rheological measurements in synovial fluid studies should be standardized.

Difficulties are encountered in estimating hyaluronic acid glucosamine, the concentration of which must be known in calculating intrinsic viscosity. Intrinsic viscosity is used as a measure of the degree of mean polymerization of hyaluronic acid, and the figures obtained do not agree with the relative degrees of polymerization suggested by the mucin precipitate types produced by acetic acid.

Preliminary investigations indicate that it should be possible to obtain a measure of degree of mean polymerization and hyaluronic acid concentration from viscosity data alone.

Discussion.—DR. DAVID H. KLING (*Los Angeles, Calif.*): Dr. Fletcher and his group have made a valuable contribution. I want to express my thanks for their assistance in permitting us to introduce the Scott-Blair viscometer into our laboratory. We found it useful for the measurement of viscosity under changing conditions of shear. It has given a more accurate measurement of relative as well as of anomalous viscosity which is not possible with the Oswald type of viscometer.

Neurology of Osteo-Arthritis of the Cervical Spine. By EUGENE NEUWIRTH, *Great Neck, N.Y.*

The varied and complex neurological and neurovascular syndromes resulting from involvement of neural structures in the cervical region by degenerative changes involving the uncovertebral and/or apophyseal (interlaminar) joints are discussed. The pathogenic significance of the osteo-arthritic spurs which develop in the uncovertebral joints is far greater than that of the apophyseal joints.

The following nervous structures may be implicated through compression and irritation by arthritic proliferations in the cervical spine:

(1) cervical segment of the spinal cord;
(2) ventral and dorsal nerve roots;
(3) vertebral nerve;
(4) sympathetic plexus surrounding the vertebral artery;
(5) autonomic fibres passing through ventral roots C4 to C7.

The sensory, motor, reflex, vasomotor, and atrophic disturbances arising from involvement of the neural structures may give rise to the following syndrome:

Cervicobrachial neuralgia (radiculalgia),
Lower motor neuron syndrome,
Shoulder-hand syndrome ("neurotrophic rheumatism of the upper extremity"),
Ocular lesions including optic neuritis,
"Intricated" and pseudo-angina,
Headaches,
Facial pains ("atypical facial neuralgia"),
Syndrome of Barré-Lieou,
Syndromes resembling those of degenerative diseases of the spinal cord (multiple sclerosis, amyotrophic lateral sclerosis, etc.).

The cardinal point of the problem is the very important question: whether there is a causal relationship between the cervical osteophytic spurs and the neurological manifestations?

Osteophytes jutting into the spinal canal or the intervertebral and transverse foramina may traumatize their nervous contents and produce neurological disturbances. On the other hand, roentgenological evidence of cervical osteophytes does not necessarily imply that they are the cause of neurological complications. Though cluttered with large osteophytes, the cervical spine of persons over 50 years old are generally asymptomatic.

It is believed that, in conjunction with the mechanical factor of compression, an inflammatory factor, particularly an inflammatory oedema within the cord and nerve roots due to irritation of the surrounding soft tissues through osteophytic spurring, brings about neurological manifestations.

It should be borne in mind, however, that even a normal roentgenogram does not preclude root involvement. "Root-sleeve fibrosis" (Frykholm) may cause radicular symptoms and signs through angulation and constriction of the cervical nerve roots in patients with roentgenologically normal cervical spines. This observation could explain the cases in which the level of the pathological change responsible for the neurological abnormalities does not coincide with the level of the osteo-arthritic lesion.

Discussion.—DR. DAVID H. KLING (*Los Angeles, Calif.*): Dr. Neuwirth should be congratulated for calling our attention to this very important group of common conditions which cannot be explained either roentgenologically or on the basis of a simple segmental pathology. When a patient with severe rheumatoid arthritis involving the cervical spine developed optic neuritis, neurological and ophthalmological consultants could not arrive at a conclusion as to the aetiology. Dr. Neuwirth's concept supplies a plausible explanation of this obscure complication and many other puzzling radicular symptoms connected with spondylitis.

Pathological Fractures during Cortisone and Corticotropin Therapy. By PAUL H. CURTISS, JR., WILLIAM S. CLARK, and CHARLES H. HERNDON, *Cleveland, Ohio.*

The development of severe osteoporosis with pathological fractures is now a recognized hazard of prolonged treatment with cortisone. Such fractures have been reported, but principally in female patients of the post-menopausal age group. The fact that this complication is not predominantly influenced by age or sex is illustrated by four cases to be presented. These patients were males with typical rheumatoid arthritis whose ages ranged from 9 to 67 years, and who had received cortisone or corticotropin continuously or intermittently for periods of 1 to 4 years. Each developed vertebral fractures of varying extent and severity without known trauma. The precise role of cortisone or corticotropin

in the genesis of the fractures could not be determined. Calcium, phosphorus, and nitrogen excretion is known to be increased during cortisone and corticotropin administration, during immobilization, and during the course of active rheumatoid arthritis. All these factors were present in these patients, but it is reasonable that hormone treatment was mainly responsible.

Although phosphorus, calcium, and nitrogen excretion is decreased by oestrogens, androgens, and physical activity, no therapeutic or preventive measures have been proved effective against pathological fractures of this type.

Discussion.—DR. EDWARD F. ROSENBERG (*Chicago, Ill.*): I regret to say that this is a subject on which I am rapidly becoming well informed.

Compression fractures of the vertebrae, transverse fractures of the neck of the femur and fractures of the humerus, radius, ribs, and tibia, have occurred among our patients receiving hormone treatment for rheumatoid arthritis. Yet it is only fair to recall that during the pre-cortisone era fractures such as these were not unknown, also that osteoporosis is a cardinal feature of severe rheumatoid arthritis. I would say that the incidence of such fractures is higher now than before the use of hormones, but that the basis for them is the same as before the advent of this method of treatment.

I do not think this is any indictment of hormone therapy, and I am not in agreement with the recommendation that we are constrained to withdraw cortisone or ACTH if a fracture occurs. I prefer to institute proper treatment for the fracture and at the same time to continue treatment with the hormones.

I venture to predict that, should we be fortunate enough to develop the "ideal" therapy for rheumatoid arthritis, we should see even more fractures than we do now. The nature of this disease is such that when the patient becomes active he exposes his weakened skeleton to stresses beyond the tolerance of his fragile bones. In these circumstances fractures are inevitable.

The hope of bringing relief from the terrible suffering which accompanies rheumatoid arthritis should be sufficient to justify a calculated risk.

We may expect that resumption of normal activity may encourage restoration of strength to the atrophic skeleton. The problem may be solved for some of the patients in this indirect manner.

This is not a simple matter of loss of calcium through hormone treatment. Our studies showed no distinctive effect on calcium balance, and our patients' blood calcium levels have been consistently normal.

It has been suggested that we should avoid using this treatment if roentgenograms show any significant degree of osteoporosis, but this would bring great hardship in many cases, for those with skeletal atrophy include individuals who respond quite well to hormones, only a small percentage of whom will suffer a fracture. We may warn all patients with osteoporosis to avoid any unusual stress such as lifting heavy objects, but we must be prepared to encounter fractures from insignificant trauma, in the performance of acts which can hardly be avoided.

For the moment, it seems to me proper to proceed cautiously, to advise every precaution possible, but at the same time to press forward with our work in this field.

DR. CURTISS: I should like to call on Dr. William Clark, my co-author, to speak about calcium excretion and the administration of hormones.

DR. CLARK: It is difficult to speak about cortisone complications without giving the impression that you are against cortisone. That is not the implication here.

Pathological fractures constitute one of the major complications of cortisone therapy. From metabolic knowledge accrued to date, it seems there are certain things that can be done to try to prevent them.

We are not presenting this paper, as Dr. Rosenberg implies, as an argument as to whether cortisone should be used or not. We are impressed because we saw all these patients within a short space of time, and we feel that the dosage of cortisone and not the disease was the major factor.

In 8 years at the Massachusetts General Hospital, I can only recall two patients with rheumatoid arthritis who developed pathological fractures, both of which occurred on the operating table in preparation for surgery. In the 18 months in Cleveland, we have seen six pathological fractures in patients on cortisone therapy. I think these patients were overdosed and that such indiscretions can result in pathological fractures of this degree. When such a complication occurs we find very little choice but to pull out of it and start all over again.

Occurrence of Spondylitis in Juvenile Rheumatoid Arthritis. By THEODORE A. POTTER, ROBERT BARKIN, and J. SYDNEY STILLMAN, *Boston, Mass.*

Spondylitis occurs more commonly in juvenile rheumatoid arthritis than was previously thought. In 61 cases there was clinical involvement in 70 per cent. and radiological confirmation in 54 per cent.

Clinical evidence is noted by loss of neck and spinal motion, developing round-back, and cervical spine extension deformity. Spinal *x* rays show the following changes:

Fusion of apophyseal joints, lateral masses, and sacro-iliac joints;
Underdevelopment of vertebral bodies, intervertebral disks and spinous processes;
Occasional subluxation of the atlas on the axis;
Lack of paravertebral ligamentous calcification.

These changes can take place in as little as 4 months. The areas most commonly involved are the cervical and sacro-iliac joints, often with no evidence of disease in the intervening spine. The average age of onset was 9·8 years with a span of 2½ to 20 years. 81 per cent. of males and 65 per cent. of females were affected.

In a few cases *x*-ray evidence of spondylitis was the only stigma of Still's disease.

Conversely, this type of survey can be helpful in establishing a diagnosis where clinical involvement of peripheral arthritis is absent.

From the orthopaedic and medico-legal aspects where spinal injury has occurred, it is most important to distinguish between traumatic fusion, congenital failure of segmentation, and juvenile rheumatoid spondylitis.

Discussion.—DR. CHARLEY J. SMYTH (*Denver, Col.*): Were there any subcutaneous nodules in any of these children?

DR. MORRIS ZIFF (*New York, N.Y.*): What is the

usual order of onset of the arthritis? Am I right in presuming it to be peripheral?

DR. RICHARD H. FREYBERG (*New York, N.Y.*): I congratulate the authors for clarifying what has been vague in the minds of many of us.

For sometime we have been seeing arthritic children with stiff necks, and thought this was caused by extra-articular rheumatism. The development of these changes indicates that many of these children have arthritis of the cervical spine. It is to be emphasized that this has quite a different type of arthritis from that seen in rheumatoid (ankylosing) spondylitis of adolescents and adults.

Some roentgenologists who see the *x*-ray films are unfamiliar with this form of arthritis, and send in misleading reports that the condition is due to congenital fusion of the spine.

DR. POTTER: In answer to Dr. Ziff's question on the order of onset, I presume that in most of these children the involvement of the peripheral joints preceded that of the spine, although it is possible that a child might have a backache for 2 or 3 months before any peripheral joint pain was noticed. We have seen that in adults with rheumatoid arthritis.

I cannot answer the question about subcutaneous nodules, but I am sure they occur.

I want to thank Dr. Freyberg for his remarks. Congenital fusion of the vertebral bodies or so-called congenital failure of segmentation present an important problem of differential diagnosis.

In congenital fusion the dorsal and cervical regions are most often affected, two contiguous vertebrae form one mass, with no evidence of disk, the striations of bone going between the bodies, the posterior elements are fused in one mass, with one large spinous process, and there is no underdevelopment of the area. With these points in mind, perhaps our radiologists could do better.

Mechanism of Anaemia associated with Rheumatoid Arthritis. By E. J. FREIREICH, J. F. ROSS (by invitation), T. B. BAYLES, C. P. EMERSON, and S. C. FINCH (by invitation), with the technical assistance of MISS C. MACDONALD, *Boston, Mass.*

A moderate anaemia refractory to anti-anaemic therapy is commonly found in active rheumatoid arthritis. We have studied:

(1) red blood cell production, utilizing radioactive iron tracer techniques;
(2) red blood cell destruction by faecal urobilinogen measurements;
(3) red cell survival with the Ashby technique of differential agglutination.

(1) An injected tracer dose of radio-iron was rapidly removed from the plasma of these patients. The serum iron concentration, however, was depressed so that the calculated iron turnover rate was within the normal range. External monitoring over major body organs showed that the largest fraction of radio-iron cleared from the plasma was deposited in the bone marrow and subsequently discharged into the blood. 80 to 95 per cent. of the injected radio-iron was utilized for red cell formation in 7 to 10 days. Thus the rate of red cell formation was within the normal range.

(2) The quantity of haemoglobin destroyed per day, as calculated from faecal urobilinogen measurements, was within the normal range.

(3) Normal donor cells transfused into rheumatoid arthritis patients showed a decrease in their effective lifespan. In contrast, red cells from rheumatoid arthritis patients transfused into normal recipients survived normally. Thus these patients produce a red cell capable of normal survival, but may have an extracorpuscular haemolytic system not associated with any identifiable immune mechanism responsible for a decrease in the lifespan of red cells.

Although these patients had a normal rate of erythropoiesis, the shortened red cell survival resulted in a decreased red cell mass. The marrow fails to increase its rate of red blood cell production.

Discussion.—DR. JOSEPH J. BUNIM (*Bethesda, Md*): Dr. Bayles and his associates are to be congratulated for this very well conceived and admirably executed study. It is encouraging to report that our results of work done mainly by Dr. Frank Ebaugh, Jr., and Dr. Ralph Peterson are essentially in agreement with theirs.

There is one slight difference, however, that may perhaps be resolved with further studies and more patients. We have transfused the red blood cells from two patients with rheumatoid arthritis into two separate normal recipients. In one case the survival time was normal in the recipient, although it was abnormally short in the patient. But in the second case, when the cells were transfused to the normal recipient, the rate of destruction was unaltered, *i.e.* it was just as abnormally high as in the patient. That may have been because some substance responsible for the destruction was so firmly attached to the transfused red blood cell as not to be separated, despite repeated washing.

I think the important ground of agreement is that the anaemia seen in rheumatoid arthritis is not an iron deficiency anaemia, but results from increased destruction without adequate compensatory production.

In a diagram of our results the rate of cell destruction compared with the normal is represented by a red column. This rate was determined by survival time, not by the Ashby selective agglutination technique used by the Boston group, but by tagging these cells with radioactive chromium.

Having determined the rate of destruction and knowing the red blood cell mass in the patient, the rate of production was calculated. A green column shows this rate of production compared with normal. In three patients with active rheumatoid arthritis the rates of destruction and production were essentially the same, so that they had an almost normal haematocrit of 42, 42, and 42.

In almost every case of active rheumatoid arthritis (eleven patients), the rate of destruction is greater than normal, but the rate of production does not rise adequately. As a result, anaemia develops and the haematocrit falls to 35, 31, and 34.

One particular patient had a mild bout of arthritis and the rate of production of cells was almost as rapid as the rate of destruction. Suddenly, without known cause, he had a severe spontaneous exacerbation. The rate of destruction rose to twice normal, and the rate of production was unable to keep up with it. Within 2 months the haematocrit fell from 42 to 34, and we know that there was no blood loss.

A second patient showed the opposite effect. She entered the hospital in a very severe and active rheumatoid

state, the rate of destruction being three times the normal. The rate of production was only twice the normal, with a resulting anaemia and a haematocrit of 24. Then the rheumatoid activity subsided without any specific medication, and although the rate of destruction was still twice the normal, the rate of production was also about twice the normal, so that the haematocrit rose to 40.

DR. A. ST. J. DIXON (*Boston, Mass.*): Dr. Freireich and Dr. Bayles have clearly shown, as Dr. Bunim and his colleagues have also shown, that decreased red cell survival is a factor in the production of the anaemia of rheumatoid arthritis in some cases.

We, on the other side of Boston, wondered how far this anaemia was due to increase in plasma volume or to decrease in red cell mass. We took a series of ten typical rheumatoid arthritis patients, all women, between the ages of 35 and 65 and matched them as closely as we could with ten normal women. We measured the plasma volume by the Evans blue method, and simultaneously measured the red cell mass by the radioactive sodium chromate red cell tagging method (Sterling and Gray, 1950).* Ten of the patients and eight of the normal subjects were confined to bed at the time of the test. As expected, the ten rheumatoid patients showed an increased proportion of plasma to red cell mass, and, were hence more anaemic than the normal controls, but, to our surprise, most of this decrease in haematocrit was due to a 22 per cent. increase in the absolute plasma volume which was statistically significant (Table). A 5 per cent. decrease in red cell mass was not significant. There was also a significant increase in total blood volume.

TABLE

Subjects	Ten Normal Women (± standard deviation)	Ten Arthritic Women (± standard deviation)	Difference (± standard error)
Plasma Volume (ml. per sq. m.) . .	1,452±110	1,767±204	314± 73*
Red Cell Mass (ml. per sq. m.) . .	926± 71	868±110	−58±132
Blood Volume (ml. per sq. m.) . .	2,379±134	2,636±232	257± 86*

*difference significant.

One trouble in making comparisons between patients and controls arises in choosing the standard of references by which they are compared. We have used surface area here. To have used body-weight would have introduced an error because the normal blood volume per unit weight increases as weight decreases, and our patients were significantly less heavy than the controls. Estimates of surface area, however, depend on height, and we had difficulty in measuring height in patients who had flexed knees and in others who were confined to bed. Consequently, I have recalculated these figures, assuming an average underestimate of height of 2 inches. Even this does not affect the validity of these results. The plasma volume is still significantly increased, and the difference in red cell mass does not reach significance.

It seems, therefore, judging from these figures, that the anaemia of rheumatoid arthritis is at least partly due to increase in plasma volume, but I must emphasize the need for caution in extrapolating from one series of selected patients to the population of rheumatoid arthritis as a whole. Other contributing factors such as decreased red cell survival are by no means excluded.

DR. BAYLES: In answer to Dr. Bunim: the sicker patients are more apt to show increased red blood cell destruction.

In answer to Dr. Dixon, the plasma volume of sick people is generally hydraemic and this certainly plays a part. We feel that there is a curious mechanism here, in that the patient, or rather his bone marrow, does not have the ability to respond to the lowered red cell mass.

* Sterling, K., and Gray, S. J. (1950). *J. clin. Invest.*, **29**, 1614.

Action of Uricosuric Agents on Discrete Renal Functions, with special reference to Effects on Uric Acid Excretion in Gout. By ALEXANDER B. GUTMAN, JONAS H. SIROTA, and T. F. YÜ, *New York, N.Y.*

Better insight into the mechanisms of action of uricosuric drugs is desirable because of their current use in the management of gouty arthritis. The present report summarizes acute and protracted renal clearance studies during probenecid, phenylbutazone, and salicylate therapy in gouty subjects.

Probenecid in a daily oral dosage of 1 g. increases the mean urinary urate excretion by approximately 50 per cent., with corresponding falls in serum urate. This is due to a sharp increase in C urate/C inulin occurring within 40 minutes after one 2-g. oral dose, reaching a mean 4-fold peak in about 2 hours, and persisting about 24 hours. There is no significant effect on GFR, C_{Po4}, C_K; sometimes a slight increase in C_{Na} and C_{Cl}; C_{PAH} is depressed.

Phenylbutazone has a uricosuric effect only at blood levels > 10 mg. per cent. After intravenous injection (12-27 mg./Kg.), C urate/C inulin rose within 2 hours to a mean 3-fold peak, uricosuria persisting about 24 hours. GFR unchanged or lowered; C_{PAH}, C_{Na}, C_{Cl} were depressed; C_K was unaffected. After oral administration, uricosuria usually occurred but was variable in onset and magnitude.

The renal effects of salicylate are more complex. Plasma salicylate levels > 5 mg. per cent. lower C urate/C inulin; levels > 12 mg. per cent. cause a mean peak 3½ fold rise in C urate/C inulin, of short duration; intermediate plasma salicylate levels have little or no effect. Concomitant bicarbonate infusion increases C urate without affecting C inulin when urinary $pH > 7{\cdot}5$, and excreted salicylate exceeds filtered salicylate, suggesting tubular secretion of salicylate.

Probenecid is best tolerated clinically in oral doses, and is the most potent and selective uricosuric agent examined.

Discussion.—DR. E. R. HUFFMAN (*Denver, Col.*): I should like to show the salient features of our results using oral phenylbutazone.* The serum and urine urate after 8 days' oral administration of phenylbutazone in gouty and non-gouty arthritics, showed a maximum decrease of 3·6 mg. (42 per cent.). The non-gouty subjects had a smaller decrease (2·4 mg.), but the percentage change was the same (42 per cent.).

The urinary urate in gouty subjects showed a mean increase of 204 mg. per 24 hrs above the control value

* Full article on p. 317 of this issue.

compared with 69 mg. per 24 hrs in the non-gouty subjects.

One gouty patient and two non-gouty patients had a mean decrease in the urinary urate while under therapy; in spite of a decreased output, they averaged a 1 mg. per cent. decrease in serum urate. All three subjects showed marked fluid retention. Our observations for the gouty subjects were significant.

When our data on the effect of 8 days' oral administration of phenylbutazone on the serum urate and renal clearance of urate was summarized, we found the clearance in the gouty subjects increased by 9·5 ml. (177 per cent.), and that of the non-gouty subjects by 8·3 ml. (115 per cent.). The clearance ratio $\frac{C_{ur}}{C_{cr}}$ showed an increase of 257 per cent. in the gouty and 115 per cent. in the non-gouty subjects.

Those with phenylbutazone levels below 10 mg. per cent. showed an increase in the clearance ratio, $\frac{C_{ur}}{C_{cr}}$ of only 48 per cent., while those with serum levels above 10 mg. per cent. showed an increase of 346 per cent.

Serum phenylbutazone levels were also determined in 73 instances after 8 days' oral administration; each increment in dosage up to and including 600 mg. per 24 hrs produced a marked increase in the serum phenylbutazone level compared with the effect of similar increments above 600 mg. For example, increasing the phenylbutazone dosage from 200 to 600 mg./24 hrs resulted in an increase in the serum level of 7·2 mg. (115 per cent.); a similar increase in dosage from 600 to 1,000 mg./24 hrs resulted in an increase of only 2·5 mg. (10 per cent.).

Ten out of thirteen subjects receiving 600 mg. daily, and all who received dosages above this amount, showed serum levels above 10 mg. per cent.

These data indicate that orally administered phenylbutazone is a uricosuric agent. It is noteworthy that in three out of nineteen subjects the serum urate level decreased, while the urinary urate level remained steady. All manifested a marked weight gain and other findings associated with fluid retention.

Dosages of 600 mg. or above are necessary to produce serum phenylbutazone levels greater than 10 mg. per cent., and serum levels above 10 mg. per cent. are necessary to produce a marked uricosuric effect.

DR. WILLIAM H. KAMMERER (*New York, N.Y.*): Dr. Gutman, I wonder if your group has been able to study the effect of Benemid in any of the siblings of patients with clinical gout who may also have hyperuricaemia.

DR. GUTMAN: I should like to thank Dr. Huffman for this additional data.

In answer to Dr. Kammerer: we have not given Benemid to asymptomatic siblings of gouty subjects. We should expect that anyone with hyperuricaemia would show a similar response, whether presenting clinical symptoms or not.

Intravenous Colchicine in the Management of Gouty Arthritis. By WALLACE GRAHAM and JAMES B. ROBERTS, *Toronto, Canada.* (Paper read by Dr. Donald C. Graham.)

The intravenous administration of colchicine is worthy of a much wider application where a rapid response is required and where severe gastro-intestinal intolerance prohibits oral medication.

Colchicine was administered intravenously to 41 patients suffering from acute gouty arthritis. The majority experienced a rapid and dramatic relief from pain within 4 hours. No toxic reaction was observed after a single dose of 3 mg., but after repeated administration gastro-intestinal manifestations may occur.

Intravenous colchicine has proved to be a safe, rapid, and effective weapon in the acute phase and deserves much wider recognition. The administration is a simple office or home procedure. The prophylactic and therapeutic value of the intravenous route in surgical patients should be noted.

Phenylbutazone (Butazolidin) was also used orally and intramuscularly.*

Discussion.—DR. WILLIAM H. KAMMERER (*New York, N.Y.*): We have used intravenous colchicine for the past 15 years in our practice and have found it a very efficacious agent in the treatment of the acute attack. Over and above that, however, I think it has another advantage, and that is as a therapeutic test in a patient with an acute monarticular synovitis, particularly in the male. Here it may help in diagnosis because, as Dr. Graham has pointed out, the results from colchicine are rather specific and, in a large percentage of cases, positive. It offers an obvious advantage over phenylbutazone.

DR. CHARLEY J. SMYTH (*Denver, Col.*): I should like to congratulate our essayists for a most delightful review of the historical aspect of this subject.

We have had some experience in the last 3 years with phenylbutazone given by oral doses, ranging from 100 to 200 mg. in acute gout. In every instance, in thirty acute attacks in 27 different patients, we have had complete abortion of the acute attack within 8 hours. None of these patients had any particular change in the serum uric acid level at the end of 8 hours, and we had no significant toxicity.

We think that the oral use of Phenylbutazone holds considerable promise.

DR. HOWARD F. POLLEY (*Rochester, Minn.*): Drs Ward, Slocumb, Hench, and I wish to confirm Dr. Graham's report on the effectiveness of colchicine administered intravenously for acute gouty arthritis. We have given several hundred injections with satisfactory and encouraging results. The preparation and its method of administration are well tolerated. In most instances only a single injection is needed; rarely are more than two doses required. We have generally used doses at least as large as those given by Dr. Graham and his associates. Occasionally larger doses, up to 5 ml. and even up to 10 ml. in selected cases (colchicine 0·65 mg./ml.), have been used. Even these doses have been well tolerated except for the infrequent occurrence of temporary gastro-intestinal upset when the large doses were given. I believe that none of our patients had nausea, vomiting, or diarrhoea from doses of 3 mg. or less, such as those used by Dr. Graham. One patient has had more than 100 doses of 5 to 10 ml. each over a period of 2 to 3 years without signs of intolerance or refractoriness to colchicine.

We have found the intravenous preparation of colchicine especially suitable for post-operative attacks of gouty arthritis. The risk of gastro-intestinal upset from the oral use of colchicine generally is so great that

* See also *Annals of the Rheumatic Diseases* (1953). **12**, 16.

surgeons and physicians are unwilling to give it by mouth after operations.

In so far as I am aware, a preparation of colchicine for intravenous administration of this concentration is not on the market in this country. Our supply is made in the laboratories at the Mayo Clinic from pure crystalline colchicine obtained from Abbott Laboratories. I should like to ask Dr. Kammerer or the other discussers who have used colchicine intravenously where they obtained their preparations. Perhaps members of our society could individually or even collectively encourage our friends in the pharmaceutical industry to make a preparation of colchicine suitable for intravenous use generally available to the medical profession. I think such an effort would benefit our patients with gouty arthritis.

DR. JACOB S. KOMINZ (*Rochester, N.Y.*): In answer to Dr. Polley, I represent no drug house, but Parke Davis sent me a big supply of 1-ml. ampoules containing 1 mg. colchicine. I have been using this for over a year now, with results similar to those described by Dr. Graham and Dr. Polley.

DR. WILLIAM H. KAMMERER (*New York, N.Y.*): The preparation of colchicine just mentioned is the one we used. I should like to utter a word of caution because there is also another preparation on the market (I have forgotten which drug house puts it up) in combination with 20 gr. sodium salicylate and 10 gr. sodium iodide. If you are using it for a therapeutic test, the 20 gr. salicylate may lead you a little astray.

DR. DWIGHT C. ENSIGN (*Detroit, Mich.*): I just want to confirm Dr. Kominz's statement that Parke Davis does have this preparation available. As I understand it, in a roundabout way, they were about to advertise it to the profession when ACTH and cortisone came out, and they then felt it was a poor time to launch another new drug. If anybody is interested in getting it, if they will address their sales manager, it will promptly be made available. We also received a gratis supply of this material, which they were about to market under the name of "Aqua-Colchin".

DR. HOWARD F. POLLEY (*Rochester, Minn.*): We have also received some of the colchicine prepared for intravenous use by Parke Davis. It has been said that they (and other companies) estimate that the cost of producing this item for general distribution would be greater than the cost of making it available as an unlisted item to those physicians who request it. In all probability, however, the intravenous use of colchicine would become more widespread if the availability of a suitable preparation were more generally known.

DR. RICHARD T. SMITH (*Philadelphia, Pa*): At the last count before I left home, we had used phenylbutazone instead of colchicine in seventy acute attacks.

When we first started using it we gave 400 mg. immediately, 200 mg. in 2 hours, and 200 mg. in another 2 hours, and the majority of the patients received benefit within 8 to 10 hours. More recently we tried to decrease the dose to half the amount, and the majority of patients have responded to that, but three or four needed the full dose. It is a good general substitute for colchicine, but one patient who failed to respond to phenylbutazone gets good results from colchicine.

DR. DONALD GRAHAM: All I want to do, sir, is thank those who discussed this paper.

Clinical and Laboratory Effect of Long-Term Intra-Articular Hydrocortisone in Rheumatoid Arthritis. By IVAN F. DUFF, WILLIAM M. MIKKELSEN, WILLIAM D. ROBINSON, and NOEL H. CHATELIN, *Ann Arbor, Michigan.*

Over a 3-year period, 1,020 serial injections of 37-50 mg. hydrocortisone have been made into 105 rheumatoid joints (sixty patients). In 53 joints (50 per cent.) worthwhile benefit was achieved; in ten knees the injections were combined with orthopaedic measures to overcome flexion contractures. In fifteen other joints benefit was eventually prolonged for 17-34 days before a repeat injection was required. Upon discontinuation of therapy, benefit has persisted from 4-12 months in 19 per cent. of all treated joints. In twelve knees (seven patients) local remission of active inflammation accompanied improvement in untreated joints, but control of the arthritis in the knees of two patients, with maintenance of weight-bearing, may have contributed to rapid hip-joint deterioration.

Treatment of 32 joints (31 per cent.) was eventually discontinued because partial initial benefit could not be further improved. Decreasing local responsiveness to the steroid was observed in four joints. In twenty joints (19 per cent.) there was no clinical response to hydrocortisone. Ten individuals refused repeated injections because of discomfort or failure to achieve benefit.

Synovial fluid from 35 knees was repeatedly studied. As previously reported, local hydrocortisone may produce remarkable alterations toward normal in joint fluid. These changes generally parallel the clinical effect but dissociation was apparent in 29 per cent. Maintenance of joint fluid improvement was usually dependent upon repeated steroid injection. The alterations in synovial fluid were followed in seven joints from the active inflammatory stage into remissions developing during the months of hydrocortisone administration and which have persisted for upwards of 16 months after steroid withdrawal.

Discussion.—DR. JOSEPH L. HOLLANDER (*Philadelphia, Pa*): Several points in this excellent paper bring out some things we have been interested in for years.

One is this matter of the optimum dose. Dr. Duff and Dr. Robinson have worked out, as we have, that the optimum dose is between 25 and 37·5 mg. As Dr. Dougherty demonstrated in his connective tissue work, there is an optimum dose level. Too much can give not only no greater response but even a diminished response. We have seen that, too. Perhaps Dr. Duff has seen such over dosage and may want to describe it.

Secondly, the matter of decreasing effectiveness from repeated injections. We have seen that, too. We have found that in such cases a change to hydrocortisone tertiary-butyl acetate will often renew the effectiveness of the hydrocortisone acetate.

Thirdly, this matter of injections producing damage to the joints. Dr. Duff reported two or three patients who had been kept ambulatory by this method and then developed increasing degeneration in the hip joints. We have also seen that in a few cases. We have also followed quite a few of the knee cases by *x* ray to see how much increase in damage there was, or whether osteoporosis was produced by this method, as it often is by large doses

systemically. We have not seen osteoporosis produced by intra-articular hydrocortisone.

Lastly, the matter of relapse and sustained benefit. We feel there is some sustained benefit even when we discontinue the hydrocortisone injections in many cases. But we feel the method is most useful as an aid to facilitating rehabilitation, maintaining function, and making orthopaedic correction of deformities more rapid and effective.

DR. DUFF: The optimum dosage of intra-articular hydrocortisone is not very adequately defined. Observations reported in this study indicate that serial injections of hydrocortisone acetate at the 10-mg. level are capable of achieving definite improvements in synovial fluid characteristics, but without obvious clinical benefit. Repeated dosages at the 25-mg. level have been associated with clinical benefit as well as favourable joint fluid alterations. Dosages in the 25- to 50-mg. range are routinely employed for intra-articular injections in our clinic. There is no evidence to our knowledge that dosages in excess of 50 mg. offer any particular advantage.

Attempt to produce Experimental Arthritis with Synovo-Toxic Antiserum tagged with I^{131}. By CUTTING B. FAVOUR, JOEL C. GOLDTHWAIT, and THEODORE B. BAYLES, *Boston, Mass.*

Interest in the Masugi type of experimental nephritis which has been successfully studied with isotope-tagged antisera prompted this investigation of arthritis. Normal guinea-pigs were exsanguinated and their carcases perfused with saline. Pooled synovial tissue from several animals was extracted with saline buffered at different *p*H levels and the cell-free supernatants used to produce an anti-joint serum in rabbits. "Immune" rabbit plasma was fractionated by Cohn's cold alcohol technique and the various fractions tagged with I^{131}. These were then injected into normal guinea-pigs. At various intervals between a few hours and 3 weeks animals were killed and the radioactivity of joints and various organs determined. Other animals were held for observation during longer intervals. Analysis of tissue samples, of local histology, and of surviving animals indicates that no damage or specific localization of an isotope tag on the joint tissue took place. Since care was taken to repeat for joint tissues that which can be done for nephritis, some doubt is cast on the specificity of the experimental nephritis model. Of more importance, no evidence has been found that arthritis is the result of an antibody directed against joint tissue.

Discussion.—DR. J. ALBERT KEY (*St. Louis, Mo.*): We have started some experiments similar to the first group without tagging our joint antigens. Those experiments will be dropped as soon as I get home because I think the authors have proved that one cannot sensitize an animal with joint tissue and then inject joint tissue into the circulation and produce inflammation in the joints.

I have been interested for quite a long time in trying to produce an Arthus-phenomenon in a joint. We used egg albumen and horse serum, or dog serum, rather. We produced a transient arthritis just as has been shown, but as soon as the acute inflammatory reaction subsided the joint tended to return to normal, unless irreversible changes had occurred.

BOOK REVIEWS

Textbook of Orthopaedic Medicine. Vol. I, Diagnosis of Soft Tissue Lesions. By James Cyriax. 1954. Pp. 692, 128 illus. Cassell, London. (45*s*.)

Had Dr. Cyriax in this book confined his work to the subject matter of his sub-title, he would have performed a valuable service, for there are interesting points in his method of physical examination and in his elucidation of disorders of muscular function and of peri-articular lesions. As it is, we find this work one of the most exasperating that has come our way. We must admit at the outset that we were disturbed by the publisher's note that "this is the first book in the world literature to describe a valid system for examining in isolation each function of joint, ligament, bursa, dura mater, nerve sheath, muscle, and tendon: the criteria distinguishing each disorder are set out in detail". There is no place for such hyperbole in present-day medical publication, and, of course, such extravagant statements are in no way borne out by a careful study of the book itself. This work is verbose, repetitive, and illogical. Examination, diagnosis, and treatment are hopelessly muddled in sequence. Although the work is concerned with soft tissue lesions, much time is spent upon the pathology and treatment of bone and joint disorders, with most unsatisfactory conclusions. Don Quixote-like, Dr. Cyriax tilts at imaginary enemies and exposes himself pitiably.

His writing contains many inconsequential asides, as may be seen in his discussion of obsolescent and future treatments for intervertebral disk lesions and the treatment of other lumbar disorders. Dr. Cyriax suggests, as a new idea, "a method of arthrodesis using a wedge of bone introduced between two spinous processes"; a method that has been in use in many hospitals throughout the world for some years! We do not know who is the *Debeyre*, to whom he has ascribed anterior arthrodesis by the abdominal approach. As far as we know B. H. Burns was the first to carry out this operation, and amongst other advocates have been Mercer of Edinburgh and Merle d'Aubigné of Paris. Throughout this book inadequate recognition has been given to orthopaedic surgeons for their contributions to physical medicine. Furthermore, although many authorities are quoted, there is no bibliography.

Dr. Cyriax without doubt is an amusing and forceful teacher of physical medicine, but in this book he has done nothing to sustain his argument for the establishment of a department of orthopaedic medicine, which doubtless would include the manifold medical interests of diseases such as bone and joint tuberculosis, osteomyelitis, infantile paralysis, metabolic disorders of the skeleton, and even rheumatoid arthritis, subjects which from an orthopaedic and medical point of view are in his book only very slightly touched upon. One realizes that none of these are purely soft tissue lesions, but then neither are the intervertebral disk lesions about which so much of the book expands.

Dr. Cyriax has missed a great opportunity. He had something important to give in teaching a proper method of physical examination, and his book would have been valuable if, a quarter of its present size, he had eliminated the nonsense.

NORMAN CAPENER.

Espondilite Anquilosante (Ankylosing Spondylitis). By Jacques Houli. 1954. Pp. 109, 16 illus. Editôria Capitólio, Rio de Janeiro.

This short monograph may be regarded as a reasonably comprehensive account of orthodox views on ankylosing spondylitis. One of the author's main aims in publishing it—and we must congratulate him on this—was to make a plea for its early diagnosis as the one hope of preventing chronic invalidism. It is strange to find him stating that this disease is known as "juvenile spondylitis" in England, but he makes thorough amends for this error by rejecting the American view that the condition is a form of rheumatoid arthritis. Each chapter contains a resume of modern methods of diagnosis and treatment, etc., comparing them with the author's findings in 25 of his own cases. Although aware of the limitations of cortisone, he regards it as one of our strongest therapeutic weapons. It is a pity there is the odd serious mistake such as the statement on p. 30 that rheumatoid arthritis is commoner in males. Photographs of some typically advanced cases are included, but the *x*-ray reproductions are generally poor, and it is surprising to find no index. On the whole, however, the book is fairly well balanced and it is easy to read.

PAUL B. WOOLLEY.

Arthritis and Rheumatism: The Diseases and Their Treatment. By Charles L. Steinberg and five other contributors. 1954. Pp. 309. Springer, New York. ($10; 70*s*.)

The primary purpose of this book, as stated in the preface, has been to emphasize the everyday responsibilities and functions of the physician who cares for arthritic and rheumatic patients. That this aim has not been fully achieved is evident from the fact that degenerative joint disease is dealt with in four pages. The chapter on basic and comparative physiology of joints forms a useful and adequate introduction to the subject; included in this is a discussion on the composition of joint fluid such as is rarely found outside the comprehensive works on the subject. It is surprising, however, that no mention

is made of the value of differential white cell counts on synovial fluid, apart from a somewhat misleading statement in a later chapter that the "presence of many polymorphonuclear cells usually indicates a specific bacterial infection rather than rheumatoid arthritis".

In the course of a comprehensive discussion on the pathology of rheumatoid disease the inclusion of collagen disorders is in keeping with the present tendency to bring these disorders within the scope of the rheumatologist. This chapter is profusely illustrated with excellent microphotographs, several of which are in colour. The authors point to the increasing frequency with which L.E. cells are found in rheumatoid arthritis and raise the problem of the relationship between disseminated lupus erythematosus and rheumatoid arthritis, but not all will agree that disseminated lupus erythematosus is unrelated to chronic lupus erythematosus.

Rheumatic fever is discussed from several aspects, particular attention being paid to the clinical manifestations and much recent work is included in the sections on treatment with cortisone, prophylaxis and prevention.

The section on rheumatoid arthritis comprises nearly 50 pages and gives an up-to-date picture under the headings aetiology, pathogenesis, pathology, symptoms, therapeutic criteria, classification of stages, differential diagnosis and treatment. This latter section includes a discussion on gold therapy, special attention being paid to the toxic disturbances and their treatment. Methods of administration of cortisone and hydrocortisone are discussed, due attention being paid to several recent papers, but no mention is made as to the selection of suitable patients for the exhibition of these substances. Due consideration is given to the relative and absolute contra-indications. The importance of infection and surgical procedures and the management of patients receiving hormone therapy is stressed.

There are short sections on variants of rheumatoid arthritis, rheumatic syndromes and uncommon joint disorders such as fluorosis and hydralazine (Apresoline) arthritis. The inclusion of this pharmaceutic arthritis is proof of the admirable co-operation between author and publisher, since the report referred to appeared in the literature only a few months before this book was published. Orthopaedic treatment is discussed in some detail as an adjunct to medical care and physiotherapeutic measures.

A valuable chapter on physical medicine treatment includes such important topics as the place of therapeutic and prophylactic exercises with considerable detail as to the ideal extent of such movements for each joint. A very practical section is devoted to rehabilitation, not in the usual vague terms but with particular emphasis on the patient's return to his place in society, his functioning within the limits of his disability and to the best of his capabilities. To this end many simple self help devices are described.

In a book so profusely illustrated, including many in colour, it is disappointing to find so few x-ray productions and these of poor quality.

R. I. MEANOCK.

Connective Tissue in Health and Disease. Edited by G. Asboe-Hansen. 1954. Pp. 321. Munksgaard, Copenhagen. ($7.50; DAN. KR. 50.)

The connective tissues have been studied intensively in recent years by physicists, chemists, biologists, and pathologists. At the same time there has been a new interest in the rheumatic diseases, and the rheumatologist —although still mainly concerned with joint disease—is becoming increasingly a specialist in connective tissue disorders of all kinds. In the future someone may write a text-book of rheumatology in the widest sense, dealing with the subject in terms of connective tissue mechanisms, but the gap between the fundamental studies of connective tissue and the problems of disease in patients has not yet been bridged.

Great advances have been made in recent years. Connective tissue metabolism which was a closed book five years ago is now an established and rapidly expanding subject. New methods have been introduced for the isolation and characterization of connective tissue components and connective tissue changes are explored by histochemical techniques and biophysical analysis; but we are still at the stage of analysis and few attempts have been made to integrate new knowledge and to develop concepts that might be useful to the clinician. Those who hope to find such a synthesis in Dr. Hansen's work will be disappointed.

The present volume is not so much a book as a collection of independent reviews by accepted authorities. Thus, Karl Meyer presents his views on the chemistry of the ground substances and Dorfman gives us a very up-to-date review of the metabolism of mucopolysaccharides dealing fully with new work using C_{14}-labelled acetate. The really new piece of information is that on the basis of these studies hyaluronic acid appears to have a metabolic half-life of only two days. The histochemistry of connective tissue is reviewed by McManus and spreading is discussed by Duran-Reynals. As one would expect from the editor's interest, polysaccharides and mast cells are fully dealt with; but the chapter on collagen is very sketchy and elastin receives little consideration. There are also reviews dealing with ageing, wound healing, and the influence of hormones on connective tissue, and there is an account by Rinehart of the arteriosclerotic changes produced in monkeys by pyridoxine deficiency. Many of these reviews are clearly intended for the specialist and are a useful source of up-to-date information. On the other hand, the vast subject of arthritis has been dismissed in nine pages, and dermatology and ophthalmology receive similar treatment, so that these clinical chapters are really only of interest to non-medical readers. There is a good opening chapter by Robb-Smith on morphogenesis and there are many other excellent contributions. We should be grateful to Dr. Asboe-Hansen for collecting so many useful reviews into one volume, but not all the reviews are of equal quality, some references are inaccurate, and the volume sent for review contains four doubly printed pages which are quite illegible.

Perhaps the time is not yet ripe for a clear and integrated account of the connective tissue in health and disease.

J. H. KELLGREN.

Funktionelle Röntgendiagnostik der Halswirbelsäule. By C. Buetti-Bäuml. 1954. Pp. 160+viii, 154 figs. Georg Thieme Verlag, Stuttgart. (D.M. 42.)

Although this book is printed and published in Germany it is Swiss in origin (from the University of Basel) and won the Jubilee Prize of the Swiss Radiological Association in 1952. It is a comprehensive radiological study of the cervical spine in health and in degenerative disease and trauma; films depict the spine at "rest" and in flexion, extension, rotation, and side-flexion. The movement of each vertebra (measured in degrees from the vertical plane) has been calculated in healthy young adults, and this gives a quantitative standard for comparison in assessing the loss of function in pathological processes. Of particular interest is the chapter which deals with the *x*-ray appearances of the cervical spine in wrestlers, whose necks are liable to be subjected to unusual stresses. Although these men were symptom-free the degree of spondylosis present was out of all proportion to age.

The photographs are excellent and the paper of first-class quality. In spite of minor blemishes, such as the absence of an index, the book will prove to be of interest to all those whose work brings them into contact with *x*-ray films of the cervical spine.

DAVID PREISKEL.

HEBERDEN SOCIETY

Heberden Oration.—Dr. R. M. Stecher of New York, who delivered the Heberden Oration on September 24, 1954, took as his subject "Heberden's Nodes". The oration will be printed in the March, 1955, issue of the Journal.

Clinical Meeting.—At a meeting held at the Postgraduate Medical School of London on September 25, 1954, the following papers were read:

DR. MALCOLM THOMPSON (*Northern General Hospital, Edinburgh*): "Kerato-Conjunctivitis Sicca and Rheumatoid Arthritis". In a study of 210 consecutive cases of rheumatoid arthritis, thirty patients (14·3 per cent.) had symptoms and signs of kerato-conjunctivitis sicca; in sixteen these were of the mild type. Ocular complications occurred more frequently in females than in males, 6·5 : 1, and were generally associated with severe and long-standing arthritis.

Investigation of the effect of steroid hormones was made in fourteen cases. Cortisone eye drops in mild cases and sealing of the lacrimal puncta and canaliculi in severe cases was found to be the treatment of choice.

DR. G. A. K. MISSEN and DR. J. E. DUNCAN TAYLOR (*Postgraduate Medical School of London*): "Amyloidosis in Rheumatoid Arthritis. A Survey of Autopsy Material". Out of a total of 6,605 cases coming to autopsy at the Postgraduate Medical School of London during the 19-year period 1935-1954, rheumatoid arthritis was diagnosed in 48. A study of the histological material from these 48 cases revealed amyloidosis of secondary type in eight (but in two of these there existed a possible alternative cause for the amyloidosis). Liver, kidney, spleen, and adrenal were the organs most commonly affected, the first three being involved in all eight cases.

All eight cases had shown proteinuria during life; three of them had died in uraemia; in six out of eight the last blood urea level recorded was above 100 mg./100 ml.

DR. RITA LACKNER and DR. G. R. FEARNLEY (*Postgraduate Medical School of London*): "Incidence of Amyloidosis in Rheumatoid Arthritis". 183 cases of rheumatoid arthritis who attended hospital during a one-year period were screened for amyloidosis. On the assumption that the most likely clinical pointer to the presence of amyloidosis would be unexplained albuminuria, the urine of all patients was tested, the number of tests depending upon the number of attendances of each patient. Persistent albuminuria was found in 24 of those tested; in twelve it could be ascribed to involvement of the renal tract by some other pathology and in twelve it was unexplained by renal investigation. Ten of these patients were further investigated by a quantitative congo red test and/or by liver biopsy; seven patients were found to be suffering from amyloidosis. One patient died before he could be investigated and extensive amyloidosis was found *post mortem*. The incidence of amyloidosis in an unselected series of hospital patients with rheumatoid arthritis is thus about 4 per cent.

DR. G. O. STOREY (*St. Leonard's Hospital, London*): "Paraplegic Para-Articular Calcification". This condition, which is characterized by the deposition of calcium and later bone in the soft tissue around joints, usually involves the hips and knee joints. Three cases were described: two with encephalo-myelitis, and the other with a cerebral neoplasm for which craniotomy was performed.

A series of 51 patients with chronic nervous disorders showed only two cases with calcification round the hip joints and this was slight in extent. Patients with paraplegia due to trauma of the central nervous system and encephalomyelitis are particularly liable to develop this complication, which it appears to develop mainly in younger people.

The aetiology of the condition was discussed. No entirely satisfactory explanation for the development of the calcification was found.

MISS JEANETTE PIRKIS, DR. NANETTE DE COEK, DR. RITA LACKNER, and DR. G. R. FEARNLEY (*Postgraduate Medical School of London*): "Diphenylamine Reaction in Rheumatoid Arthritis". This serum colour reaction was investigated in rheumatoid arthritis, and a reasonable

overall correlation with the erythrocyte sedimentation rate (Westergren) was found. The serum diphenylamine level fell in patients treated with steroid hormones. There were unexplained fluctuations in the level which were not reflected by the E.S.R. The reason for these fluctuations is unknown. The test was therefore found to be a less reliable measure of activity and more time-consuming than the E.S.R. In only two patients with active rheumatoid arthritis and a normal E.S.R. was the diphenylamine level found to be raised.

Dr. G. R. Fearnley, Dr. E. G. L. Bywaters, Dr. R. I. Meanock, and Dr. Rita Lackner (*Postgraduate Medical School of London*): "A Comparison of Procaine and Hydrocortisone given by Intra-Articular Injection in Rheumatoid Arthritis". Ten patients suffering from generalized rheumatoid arthritis whose main disability could be ascribed to severe involvement of one knee were selected for a clinical trial. They were placed by random allocation into two groups of five. One group received four fortnightly injections of 50 mg. hydrocortisone acetate into the affected knee and the other group received four fortnightly injections of 4 ml. 2 per cent. procaine. At the end of each course there was a rest period of 2 months, after which the groups were transposed, those who had received procaine being given a course of hydrocortisone and *vice versa*. A variety of assessments were made initially and at each attendance. The most valuable were found to be the sedimentation rate, limitation of extension, joint tenderness, and walking time. Both forms of therapy gave improvement, but the overall effect of hydrocortisone was more dramatic than that of procaine.

Dr. A. Aronoff, Dr. E. G. L. Bywaters, and Dr. G. R. Fearnley (*Postgraduate Medical School of London*): "Pulmonary Changes in Rheumatoid Arthritis". The incidence of lung lesions in patients with rheumatoid arthritis was compared clinically, radiologically, and *post-mortem* with that of groups of other patients selected as controls. No specific lung lesion was found in rheumatoid patients which could be characteristically associated with rheumatoid arthritis, and the relative frequency of common pulmonary lesions such as bronchitis, tuberculosis, and bronchiectasis was about the same in the rheumatoid series as in the controls. It was concluded that if a "rheumatoid lung lesion" exists, it is not common.

Annual General Meeting.—This was held at the Royal College of Surgeons, London, on December 4, 1954. The following papers were read:

Dr. G. D. Kersley (*Bath*): "Changes in the Sacro-iliac and Peripheral Joints in Spondylitis and Rheumatoid Arthritis."
Dr. B. E. W. Mace (*London*): "Gout and Pregnancy."
Dr. Ellis Dresner and Dr. Maxwell Schubert (*London*): "Comparison of Reticulin and Collagen."
Dr. M. Keech (*Taplow*): "Digestibility of Human Skin Collagen by Collagenase in Different Age Groups and Conditions."
Dr. H. F. West (*Sheffield*): "Effect of 9-fluoro Cortisol Acetate on Adrenal Function."
Dr. J. C. Leonard (*London*): "Potentiation of Cortisone in Rheumatoid Arthritis."

A Symposium on Osteo-Arthritis was given by the following:

Prof. D. H. Collins (*Sheffield*): "Pathology of Osteo-Arthritis."
Dr. G. Loewi (*Cambridge*): "Changes which occur in Ageing Cartilage."
Dr. J. Ball (*Manchester*): "Joint Changes in Patients with Heberden's Nodes."
Mr. G. C. Lloyd Roberts (*London*): "Relationship between Symptoms and Lesions."
Mr. M. H. M. Harrison (*London*): "Changes in the Vascular Tree in Osteo-Arthritis."
Prof. J. H. Kellgren (*Manchester*): Summing up.

LIGUE EUROPÉENNE CONTRE LE RHUMATISME

THIRD EUROPEAN CONGRESS, 1955

Under the High Patronage of H.M. the Queen of the Netherlands

The Third European Rheumatology Congress will be organized by the "Nederlandse Vereniging van Rheumatologen", and will be held from June 13-17, 1955, at the Kurhaus, Scheveningen, The Hague.

Organizing Committee

Hon. President:	Dr. J. van Breemen
Chairman:	E. M. Bingen
President Scientific Commission:	Prof. Dr. J. Goslings
Secretary:	Dr. J. J. de Blécourt
Treasurer:	Dr. P. van der Meer
Secretary of the Congress:	Dr. H. van Swaay
Members:	Dr. G. van Dam E. G. van Heusden Dr. R. K. W. Kuipers F. J. F. Steiner

Scientific Programme.—This will comprise four sections. Papers will be presented by the following:

Section 1. *Rheumatic Fever*
Dr. E. G. L. Bywaters, U.S.-U.K. (*England*).
Prof. F. Coste (*France*).
Dr. P. van der Meer (*Netherlands*).

Section 2. *Connective Tissue*

Drs L. E. Glynn, R. Consden, J. Holborow, and E. G. L. Bywaters (*England*).
Prof. G. C. Heringa (*Netherlands*).
Dr. G. Asboe-Hansen (*Denmark*).
Dr. Morris Ziff (*U.S.A.*).

Section 3. *Osteo-Arthritis of the Spine and Disk Degeneration*

Prof. Sten Friberg (*Sweden*).
Prof. S. de Sèze and Dr. J. Lacapère (*France*).
Dr. P. Barceló and Dr. J. M. Vilaseca Sabater (*Spain*).
Prof. H. Junghanns (*Germany*).

Section 4. *Rheumatism and Social Medicine*

Dr. R. J. Weissenbach and Dr. F. Françon (*France*).
Prof. K. M. Walthard (*Switzerland*).
Prof. A. Masturzo (*Italy*).
Prof. E. W. Baader (*Germany*).
Drs. M. Ruelle and A. Henrard (*Belgium*).

These papers will be presented in plenary sessions. The discussions will be opened immediately after the presentation of the reports.

Members who wish to deliver short papers (maximum 10 minutes) on these or other subjects are requested to forward the titles to the Secretariat. Summaries of 100-150 words in any two of the four congress languages (English, French, German, Spanish) must be submitted before January 1, 1955. The Organizing Committee will decide the acceptance or refusal of these communications.

Film demonstrations will also be arranged, and there will be a scientific exhibition in the Kurhaus; members who wish to contribute are requested to apply before January 1, 1955. There will also be an exhibition of medical and pharmaceutical products. Interested firms may obtain further information from the Secretariat.

Social Programme.—A day excursion to Amsterdam, planned for June 15, is open to all members. A trip through the canals of the ancient city will be provided through the generosity of the Municipality of Amsterdam, and there will be an official reception by the Netherlands Government at the Rijksmuseum. On June 17 there will be a social evening with buffet-supper for all members of the Congress.

A special ladies' committee will arrange for the entertainment of the associate members.

The Committee is considering the possibility of organizing a post-congress sight-seeing tour through the Netherlands and Belgium, combined with a few scientific meetings. The tour will last about seven days and members of the Congress will have the opportunity of seeing the most famous works of art of the two countries.

Registration Fee (including all social events and excursions): Active members, 100 Neth. florins (including Congress Proceedings); Associate members, 60 Neth. florins.

Exchange rates (approximate):

£1 = 10·70 Neth. florins;
$1 = 3·80 Neth. florins.

Bank.—Amsterdamsche Bank N.V., The Hague.

Accommodation.—The price of hotel rooms at Scheveningen varies from 8·50 to 32 Neth. florins, depending upon the hotel category (five classes), the location, and the bath facilities. Breakfast is always included, and for a stay of five or more days partial board can be arranged.

Further details concerning the technical programme, registration, methods of payment, hotel reservations, film demonstrations, exhibitions, entertainment, and excursions and registration forms will be supplied on application.

All correspondence should be addressed to the Secretariat of the Congress: Burg. De Monchyplein 9, The Hague, Netherlands. Tel. 185281.

CHARTERED SOCIETY OF PHYSIOTHERAPY

Annual Congress, 1954

The annual congress of the Society was held at Harrogate from September 8-12, 1954. The following lectures and discussions dealt with various aspects of rheumatology:

Prof. S. J. Hartfall: "Stress factors in the Aetiology of the Rheumatic Diseases".
Dr. W. Yeoman: "Physiotherapy in the Treatment of Rheumatic Disorders".
Mr. R. Broomhead: "Management of Surgical Treatment of Arthritis of the Hip".
Mr. H. Petty: "Orthopaedic Management of Rheumatoid Arthritis".
Mr. M. Ellis: "Soft Tissue Lesions of Ankle and Shoulder".

NUFFIELD FOUNDATION

Grants for Research in Rheumatism

During the past 5 years the Nuffield Foundation has been supporting much chemical and other work on adrenal hormones, but it is now reverting to its original policy of supporting fundamental and clinical research into the nature of the rheumatic diseases.

To the University of Manchester Rheumatism Research Centre, an additional grant of £70,000 payable over the coming 8 years is made to extend the work under the director, Professor J. H. Kellgren.

At the Northern General Hospital, Edinburgh, the Foundation is providing a new building for the Rheumatic Unit on an adjoining site to house consulting and research rooms, clinics, and laboratories, at a cost of £27,000. The new building will be ready by the end of 1954. In addition, the Foundation will continue its annual grant to assist the unit's work, and over the 5 years 1954–1958 it will provide £38,000 for this purpose.

In addition, two smaller grants have been offered to other rheumatism centres: £8,000 to the University of Sheffield to finance a research fellowship at the Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases, directed by Dr. H. F. West, and £6,000 to the Oxford Regional Hospital Board for an experimental pathologist to work on the pathogenesis of rheumatic diseases under Dr. A. G. S. Hill at the new Rheumatic Diseases Research Centre, Stoke Mandeville Hospital, Bucks.

EMPIRE RHEUMATISM COUNCIL

Course for Consultants

The British Postgraduate Medical Federation and Empire Rheumatism Council will hold a course for consultants on Modern Aspects of Rheumatic Disease at the Arthur Stanley Institute, Middlesex Hospital, and the Postgraduate Medical School, London, on March 24-26, 1955.

LIGA MEXICANA CONTRA EL REUMATISMO

Officers, 1954-1955

President:	Dr. Javier Robles Gil	*Secretary:*	Dr. Manuel Boesterly
Vice-President:	Dr. Salvador Aceres	*Treasurer:*	Dr. Armando Cuéllar

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Comparative Effects of Aspirin, ACTH, and Cortisone on the Acute Course of Rheumatic Fever in Young Adult Males. HOUSER, H. B., CLARK, E. J., and STOLZER, B. L. (1954). *Amer. J. Med.*, **16**, 168. 7 figs, 15 refs.

The comparative efficacy of aspirin, cortisone, and ACTH in the treatment of acute rheumatic fever was investigated at the United States Air Force Hospital, Wyoming. Of 148 young adult males with acute rheumatic fever admitted between January, 1951, and June, 1952, 61 received aspirin, 45 cortisone, and 42 ACTH. Full details are given of the diagnostic criteria, the investigations carried out, and the dosage of the drugs.

The results showed that fever and joint pain subsided more rapidly in the patients given aspirin than in those given cortisone or ACTH, but that otherwise there was little difference between the three drugs in their effect on symptoms. Relapse after the cessation of treatment occurred in most cases in all three groups. The authors state that the effect of the drugs on rheumatic carditis cannot be determined until the results of the long-term follow-up are known, but in each group there were cases in which new murmurs were elicited, these persisting while the patient was receiving a full therapeutic dose of the drug.

It is concluded that none of these three drugs is ideal for the treatment of acute rheumatism; indeed, in the authors' view, adequate treatment for this disease is not yet available. *Kathleen M. Lawther.*

Active Rheumatic Heart Disease in Patients over Sixty. GRIFONE, J. W., and KITCHELL, J. R. (1954). *J. Amer. med. Ass.*, **154**, 1341. 7 refs.

It is pointed out that acute rheumatic heart disease is usually seen only in children or young adults, and is often not diagnosed in patients over 60 years of age. In this paper four cases are reported from the Presbyterian Hospital, Philadelphia, in which the patients, all over 60 years, were thought to be suffering from rheumatic heart disease. One woman aged 62, who had had hypertension for 11 years, developed fever and tachycardia; the electrocardiogram showed evidence of left bundle-branch block. She died after 27 days in hospital, and necropsy revealed thickening and contraction of the mitral valve and chordae tendineae and Aschoff nodes in the myocardium. A man aged 76, with a history of pain and stiffness in the joints of 2 years' duration was admitted with fever, tachycardia, and pain in the left side of his chest. He died from bronchopneumonia and at necropsy rheumatic pancarditis was found. In the remaining two cases in females aged 74 and 68 years respectively, fever, tachycardia, and apical systolic murmurs were present on admission. The fever did not respond to treatment with antibiotics, but after administration of salicylates the temperature promptly became normal. One of these patients remained well for 2½ years, but the other subsequently required treatment for mild congestive cardiac failure. The authors consider that both patients had rheumatic carditis, though the diagnosis was not certain. *C. E. Quin.*

Commissurotomy for Rheumatic Aortic Stenosis. I. Surgery. BAILEY, C. P., BOLTON, H. E., JAMISON, W. L., and NICHOLS, H. T. (1954). *Circulation (N.Y.)*, **9**, 22. 12 figs, 11 refs.

Although a number of workers have contended that aortic stenosis is arteriosclerotic in origin, the present authors believe that it is usually the result of rheumatic infection, the commissures between the valve cusps becoming united as a result of the rheumatic process. If the condition is associated with a mitral lesion known to be rheumatic, then the probability of the aortic lesion being also of rheumatic origin is very high. The malformation present in the case of congenital aortic stenosis is of a different type and requires different surgical treatment.

At the Hahnemann Medical College and Hospital, Philadelphia, the authors have attempted to treat aortic stenosis by using a triradiate dilator (illustrated) which engages and ruptures the commissures. Of 27 patients with pure aortic stenosis so treated, six (22 per cent.) died, probably because some of the cases were really con-

genital in origin and the valve had only two cusps, while in others because the heart muscle was unduly soft. On the other hand, of 35 with combined aortic and mitral lesions, five died, a mortality of only 14 per cent., this lower figure being attributed to the smaller size of the left ventricle, which was less irritable than in the other forms.

In consequence of the dangers and difficulties associated with the transventricular approach and of the considerable discrepancy in mortality between the two groups described above, the authors have devised and carried out a retrograde approach through the wall of the ascending aorta. A pouch, which is formed by suturing a flap of pericardium to the edges of the incision into the aorta, controls bleeding and permits introduction of the valvotome. More recently a plastic pouch has been used to help in this procedure. This transaortic operation seems to be well tolerated, but the number of cases treated so far is still too small for definite conclusions to be drawn. The operation is not suitable for elderly patients, in whom the aortic wall may be friable.

T. Holmes Sellors.

Use of Dibenylethylenediamine-dipenicillin as a Prophylactic against Streptococcal Infection in Acute Rheumatism. (L'impiego della dibensil-etilendiamina-dipenicillina nella profilassi antinfettiva (profilassi antistreptococcica) della malattia reumatica.) SCURO, L. A., and ORTONA, L. (1954). *Minerva med.* (*Torino*), **45**, 1835. 3 figs, 23 refs.

Treatment of Rheumatic Fever with PAS and with a Combination of PAS and Sodium Salicylate. (Sul trattamento della infezione reumatica con PAS e con l'associazione PAS-salicilato di dodio.) BULGARELLI, R., and SARDINI, G. (1954). *Minerva pediat.* (*Torino*), **6**, 198. 3 figs.

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

Syndromes of Rheumatoid Arthritis. KERSLEY, G. D. (1954). *Lancet*, **1**, 1206. 5 figs, 21 refs.

From a wide clinical experience the author discusses, with case records, four syndromes in rheumatoid arthritis in which the differential diagnosis is based upon the mode of onset of the disease. These four syndromes are neither frequent nor a usual feature of the classic disease process—the author found one or other of them in only 67 out of a recent series of 750 cases of rheumatoid arthritis—but they are none the less distinct and individual. In 38 of the 750 cases the onset was so acute as to resemble that of rheumatic fever, but only one patient actually developed carditis. The differential diagnosis, which is discussed, is helped by the therapeutic response to colchicine, antibiotics, and salicylates. [The classification of this first group as "acute arthritis" closely resembles a major subdivision recognized in Scandinavia, in which cases of rheumatoid arthritis are divided into two groups—those with "acute" and those with "chronic" onset. The number of acute cases in this series would seem by comparison to be relatively small.] In a second group of eleven cases there was involvement of only one joint initially, and in two of these cases there was evidence of a tuberculous focus in the synovium, despite the close histological resemblance to rheumatoid arthritis. It is suggested that when tuberculous and rheumatoid foci appear in the same joint the "rheumatoid" reaction may be due to a non-specific reaction of the joint to sensitization to tuberculous infection. In a third group of thirteen cases the onset of rheumatoid arthritis was episodic, and here the differential diagnosis was from gout, palindromic rheumatism, angioneural arthrosis, allergic arthritis and intermittent hydrarthrosis. In a fourth group of five cases rheumatoid arthritis had progressed for a number of years without pain. There was gross destruction of bone and joint, but no evidence of neurological disease. Variation in the general threshold to pain or rheumatoid lesions of the perineurium were not considered to play any part.

Harry Coke.

Pulmonary Lesions in Rheumatoid Arthritis. CHRISTIE, G. S. (1954). *Aust. Ann. Med.*, **3**, 49. 8 figs, 13 refs.

The clinical and post-mortem findings in three cases of rheumatoid arthritis are described in this paper from Melbourne University, with special reference to the extra-articular lesions. In all three cases there were obvious pulmonary lesions. In one case a granulamatous mass measuring 7 cm. in diameter was found, which was indistinguishable histologically from the usual subcutaneous periarticular nodule seen in rheumatoid arthritis. The author considers that extra-articular lesions are an integral part of the disease and are present more often than is generally accepted. In the chronic stage active lesions may be found in many parts of the body, even when the affected joint is quiescent, but the scars of healed lesions may also be recognized.

A. C. Lendrum.

Systemic Lesions of Malignant Rheumatoid Arthritis. BEVANS, M., NADELL, J., DEMARTINI, F., and RAGAN, C. (1954). *Amer. J. Med.*, **16**, 197. 18 figs, 12 refs.

Although the incidence of rheumatic heart disease is said to be higher in patients with rheumatoid arthritis than in the general hospital population, there is evidence that valvulitis and other stigmata of rheumatic heart disease are infrequent in those suffering from rheumatoid arthritis except when a straightforward history of rheumatic fever can be obtained. In this paper from Columbia University, New York, is described a study of two cases of active rheumatoid arthritis complicated clinically by pleurisy and pericarditis. The duration of the rheumatoid arthritis was 10 and 16 years respectively. In the first case there were intercurrent diabetes and renal papillary necrosis, and the second patient also had epilepsy. Long-term treatment with cortisone and corticotrophin did not appear to arrest the course of the disease, and compression fractures occurred in both cases as a result of osteoporosis arising during the hormone therapy. Both patients died.

At necropsy an inflammatory obliteration of pleural and pericardial sacs was seen, together with lesions in the myocardium and valve rings due to granulomata

appearing "indistinguishable from the subcutaneous nodules of rheumatic disease". In the first case similar lesions were also found in the kidney, and in the second case in the lungs. Both patients had oesophagitis and episcleritis. The authors consider that the granulomatous lesions develop from fibrinoid necrosis of the vessel wall.

Evidence is adduced that there exists a malignant form of rheumatoid arthritis, of which the two cases described are regarded as examples. The relationship of this fulminating disease to the reputed high incidence of rheumatic heart disease in patients with rheumatoid arthritis is discussed. It is concluded that long-term cortisone therapy apparently does not prevent the development of this form of rheumatoid arthritis. *E. G. L. Bywaters.*

Citrate Iontophoresis in Rheumatoid Arthritis of the Hands. COYER, A. B. (1954). *Ann. phys. Med.*, **2**, 16. 1 fig., 7 refs.

Following the observations of Rocha e Silva (*Brit. med. J.*, 1952, **1**, 779) on the value of citrate in allergic and anaphylactic reactions, the present author, at St. Thomas's Hospital, London, used citrate iontophoresis in cases of acute rheumatoid arthritis of the hands, on the grounds that the rheumatoid process is, in part, an allergic process. He produces evidence to show that citrate may reasonably be expected to reach the affected tissues when given in this way.

One group of fifteen patients received citrate ionization, a second group of ten patients received anodal galvanism, and a third group, also of ten patients, received cathodal galvanism; the last two groups served as controls. The citrate iontophoresis was given in a cathodal bath containing 2 per cent. potassium citrate solution, a current of about 10 mA being passed for 20 to 30 minutes. In the control cases the bath contained tap-water. Patients were treated on alternate days for four weeks, and the results were assessed weekly, mainly by determining the strength of grip in the hand.

There was a much greater improvement in strength of grip in those patients treated with citrate than in the control groups. The author notes that some of the patients had previously failed to respond to more conventional methods of physiotherapy, such as wax baths and local application of heat, but that these patients tended to have a relapse when treatment ceased.

B. E. W. Mace.

Management of Rheumatoid Arthritis with Prolonged Cortisone Administration. COPEMAN, W. S. C., SAVAGE, O., DODDS, C., GLYN, J. H., and FEARNLEY, M. E. (1954). *Brit. med. J.*, **1**, 1109. 1 fig., 11 refs.

The results are presented in twenty cases of rheumatoid arthritis treated with cortisone at the West London Hospital, Hammersmith, fourteen of which received the drug for more than 2 years, and all for at least a year continuously. All twenty cases were severe, and none of the patients was able to follow his or her normal occupation. The usual methods of treatment had been tried without halting the progress of the disease. The average maintenance dose of cortisone by the oral route was 69 mg. a day, varying in individual cases from 37·5 to 100 mg. daily. No fewer than seventeen of the twenty patients improved sufficiently with this treatment to return to work.

Administration of the drug had to be stopped in two cases, in one of which severe depression occurred, and in the other the blood pressure rose from 120/80 to 200/105 mm. Hg. In three cases gastrointestinal complications (duodenal ulceration, oesophagitis associated with hiatus hernia, and melaena, respectively) developed, but it was not found necessary to discontinue treatment. Various less important side-effects were also observed.

The authors conclude that cortisone is a practical addition to treatment in selected cases of rheumatoid arthritis, but they emphasize that careful and constant supervision is necessary. *K. C. Robinson.*

Clinical Experience with a Rubidium–Gold–Creatinine-Gold Preparation in Rheumatic Diseases. (Klinische Erfahrungen mit einem Rubidium–Gold–Kreatinin-Gold-Präparat bei rheumatischen Erkrankungen.) POHL, W. (1954). *Medizinische*, No. 18, 659. 9 refs.

The preparation used in this trial carried out at the University Polyclinic, Jena, was "aurubin", which is supplied as dragees consisting of small quantities of rubidium auritetrachloride, creatinine hydrochloride and aurochlorate, and other salts. The content of gold is less than that previously used by the author, the quantity of gold administered in an 8 weeks' course of treatment amounting to only 0·306 g. The trial was conducted for a period of 3 to 4 months on 42 rheumatic patients. In general, the results obtained seemed to depend on the stage of the disease reached; it was also found that the dosage used must not be too rigid, but should be adjusted according to the reaction of the patient. A number of cases improved that had previously remained completely resistant to all forms of therapy.

Of the 42 patients, 21 were suffering from chronic polyarthritis and of these ten improved both subjectively and objectively, including three who had previously derived no benefit from the administration of cortisone or ACTH (corticotrophin). Of a further seven patients suffering from Bechterew's disease (spondylitis deformans), three responded well, as also did five of ten patients described as suffering from arthrosis. In none of the patients in a fourth group suffering from spondylosis, however, has any improvement been observed. No serious toxic effects were noted during this trial, and patients tolerated the preparation very well, only twelve patients showing some gastric disturbance and loss of appetite, two a mild diarrhoea, two rashes, and nine patients complained of tiredness. After temporarily reducing the dosage in these cases the original dose could be resumed. *Robert Hodgkinson.*

Placental Tissue Implantation for Rheumatoid Arthritis. A Preliminary Report. LINTZ, R. M. (1954). *Geriatrics*, **9**, 106. 19 refs.

At Bellevue Hospital, New York, 35 adult patients suffering from severe rheumatoid arthritis of long standing were treated by the implantation of fresh placental

tissue in the thigh, as recommended by Filatov. There was no subsequent improvement in fifteen of these cases, but in the remaining twenty there was decreased heat and swelling in the joints and increased range of movement, as well as some symptomatic improvement, starting 2 to 10 days after the operation. The improvement in five cases lasted for 3 to 4 years, in the rest for 2 to 10 months.

The author discusses the mode of action of this treatment and draws attention to the possible importance of psychological stimuli. In view of the fact that liquefied material drained from the wound in every case before closure, he does not consider that his results were due to any sustained elaboration of hormones by the implants, but points out that "this does not preclude the possibility of some short-lived hormonal stimulus from the implanted material" acting as a trigger mechanism.

G. Loewi.

Prolonged Gold Therapy. (Cristoterapia prolongada.) CARUSO, A. C. (1954). *Arch. argent. Reum.*, **17**, 47.

ACTH Treatment of Rheumatic Fever in Children. (Leczenie choroby reumatycznej u dzieci ACTH.) MARCZYŃSKA-ROBOWSKA, M. (1954). *Pediat. pol.*, **29**, 345. 16 refs.

Treatment of Rheumatoid Arthritis with Nitrogen Mustard. (Il trattamento dell'artrite reumatoide con iprite azotata.) CARTESEGNA, F., and DANEO, V. (1954). *Reumatismo*, **6**, 241. 29 refs.

Use of Ascorbic Acid in Rheumatoid Arthritis. (Considerações sóbre o uso do ácido ascórbico na artrite reumatoide.) DÉCOURT, L., LIMA, M. C., FERNANDES, J. M., and CHIORBOLI, E. (1954). *Rev. paulista Med.*, **44**, 281. 6 refs.

Role of the Vascular Factor in the Pathogenesis and Treatment of Rheumatoid Arthritis. (Die Rolle des Gefässfaktors in der Genese und Therapie der primär chronischen Polyarthritis.) PIRTKIEN, R. (1954). *Medizinische*, No. 23, 816. 2 figs, 34 refs.

Neurovegetative Reactivity of the Skin in Rheumatoid Arthritis. (Reattivita neuro-vegetativa cutanea nell' artrite reumatoide.) ROSSI, G. (1954). *Reumatismo*, **6**, 233. 26 refs.

Rheumatoid Arthritis and Heart Lesions. FERNANDO, P. B., and WIJENAIKE, W. (1953). *Indian Heart J.*, **5**, 187. 12 figs, 9 refs.

Skinfold Thickness of the Hand in Rheumatoid Arthritis. LEHTINEN, M., and TELKKÄ, A. (1954). *Ann. Med. intern. Fenn.*, **43**, 109. 4 figs, 13 refs.

Pulmonary Manifestations of "Rheumatoid Disease". HARRIS, L. H. (1954). *Lancet*, **2**, 119. 14 refs.

(Spondylitis)

Deep X-Ray Therapy in Spondylitis. SHARP, J., and EASSON, E. C. (1954). *Brit. med. J.*, **1**, 619. 2 figs, 18 refs.

Since 1947 a total of 332 cases of ankylosing spondylitis have been seen at the joint clinic of the Rheumatism Centre and Christie Hospital and Holt Radium Institute, Manchester. Of these, 242 were classified as typical, 31 as "borderline", and 59 as atypical cases. The incidence of a family history of rheumatism, iritis, or involvement of the hands or feet was not significant in any group. The present paper is concerned with results of *x*-ray therapy in 275 cases (212 typical, 28 borderline, and 35 atypical).

It was considered advisable to treat the whole spine and sacro-iliac joints in all cases. Narrow fields were applied directly and a dose of 150 r was given once a week for 10 weeks. A similar dosage was given to peripheral joints, but localized tender areas on bony points and tendon insertions received a single large dose of 500 to 600 r.

The condition of the patient was assessed before and one month after treatment. The erythrocyte sedimentation rate was not of any prognostic significance. The response to treatment was the same in males as in females, and was significantly more marked in typical cases than in atypical. There was a relapse over a relatively short period of observation in 56 of the typical cases. Complications, which were few, included aplastic anaemia (one case), reactivation of pulmonary tuberculosis (one), and renal failure (two cases). Permanent amenorrhoea developed in thirteen out of 47 females treated. The importance of exercises after radiotherapy and the dangers of immobilization are stressed.

It is concluded that only patients suffering from typical ankylosing spondylitis benefit from *x*-ray therapy. The effect seems to be directly on the tissues irradiated and not through some indirect mechanism. Further study is being undertaken with a view to establishing criteria for the differential diagnosis of atypical ankylosing spondylitis.

R. D. S. Rhys-Lewis.

Early Diagnosis and Treatment in Ankylosing Spondylitis. LYONS, A. R. (1954). *Ulster med. J.*, **23**, 34. 3 figs, 3 refs.

Skin in Ankylosing Spondylitis. (Le revêtement cutané dans la spondylose rhizomélique.) FLORENTIN, P., LOUYOT, P., MACINOT, —., and PIERSON, B. (1954). *Rev. Rhum.*, **21**, 225. 5 figs.

(Miscellaneous)

Phenylbutazone in Arthritis. DAVIES, H. R. (1954). *Ann. phys. Med.*, **2**, 8. 5 refs.

The long-term results of administration of phenylbutazone in arthritic conditions, mainly rheumatoid arthritis, are described. The drug was given by mouth in an initial dosage of 1 g. daily for 3 days and gradually reduced until the lowest effective dose was established,

which was usually 800 mg. on alternate days. Other medication, particularly with barbiturates, was avoided, and some restriction was placed on the salt intake. Determination of the leucocyte count did not appear to be necessary after the initial period of treatment.

Of 160 patients treated at hospitals in the Mid-Herts and West-Herts Hospital Group, fifteen did not benefit in any way during the initial phase, and treatment was therefore stopped. The remaining 145 patients were observed for periods varying from 3 to 18 months. It was found that while there was a definite improvement in function joint changes were unaffected. The relief of pain was the most striking result of administration of the drug, and the author suggests that its usefulness in other directions is due largely to this effect. It was of particular value in seven out of nine cases of ankylosing spondylitis. There was rapid relief of symptoms in two cases of acute gout after intramuscular injection of 1 g. phenylbutazone, while in two cases of chronic gout there was a similar, but slower, response. Marked relief of symptoms was obtained by fourteen out of thirty patients with osteo-arthritis of the hip, nocturnal pain being relieved to a greater extent than "weight-bearing" pain.

Allergic reactions to the drug in the form of a rash, angio-neurotic oedema, and mild dyspnoea occurred in fourteen cases, while twenty patients complained of gastrointestinal disturbances. Other complications included transient granulocytopenia (one case), purpura without haematological changes (two cases), and cardiac failure precipitated by fluid retention (three cases, one fatal). Two patients sustained fracture of the femoral neck while under treatment.

The author considers that phenylbutazone is a most useful adjuvant in the management of arthritic conditions, but emphasizes that continued care is necessary during long-term administration. *B. E. W. Mace.*

Observations on the Antirheumatic and Physiologic Effects of Phenylbutazone (Butazolidin) and Some Comparisons with Cortisone. BRODIE, B. B., LOWMAN, E. W., BURNS, J. J., LEE, P. R., CHENKIN, T., GOLDMAN, A., WEINER, M., and STEELE, J. M. (1954). *Amer. J. Med.*, **16**, 181. 5 figs, 22 refs.

Phenylbutazone was given to eighteen patients severely disabled with rheumatoid arthritis and to 69 non-arthritic rheumatic patients. It is pointed out that the plasma concentration of phenylbutazone does not increase commensurately with an increase in the dose but tends to approach a limit; the peak level with a daily dose of 1,600 mg. is not appreciably higher than that achieved with a daily dose of 800 mg. In the present investigation, therefore, each patient was given 800 mg. by mouth daily; later, some of the patients were given cortisone for comparison. A major improvement was noted in eight of the patients with arthritis but minor improvement only in the others. The results obtained with cortisone were similar. Side-effects were severe enough in seventeen of the 87 patients to call for cessation of treatment, but in none of the cases did agranulocytosis develop.

Phenylbutazone caused urinary retention of sodium, chloride, and water, but did not affect potassium or 17-ketosteroid excretion; in none of the cases was significant eosinopenia found. The fall in the erythrocyte count and haemoglobin level during treatment was due to haemodilution and not to depression of haematopoiesis. From their observations the authors conclude that the drug does not act through stimulation of the adrenal cortex. They consider that its anti-rheumatic effect is similar to that of cortisone and ACTH but that there is no risk of hormonal imbalance with phenylbutazone. It is hoped that these encouraging clinical results will stimulate further search for other non-steroid drugs exerting "a desirable local tissue effect".

Kathleen M. Lawther.

Clinical and Experimental Study of the Anti-rheumatic Activity of Amidopyrine Gentisate. (Ricerche cliniche e sperimentali sull'attivita antireumatica del gentisato di amido-pirina.) MAINOLI, S., and PICCINELLI, O. (1954). *Minerva med. (Torino)*, **1**, 787. 1 fig., 37 refs.

Amidopyrine gentisate (associated with amidopyrine and a synthetic antihistamine drug in a commercial preparation, "pirisal") was given experimentally at the Institute of Clinical Medicine and Therapeutics of the University of Pavia to fifteen normal subjects, five patients with acute articular rheumatism, ten with rheumatoid arthritis, seven with chronic rheumatism following acute arthritis, ten with lumbar osteo-arthritis, eight with "rheumatic myalgia", and three with humero-scapular peri-arthritis. It was given by mouth in doses containing 2·375 g. amidopyrine gentisate and 0·375 g. amidopyrine or by intramuscular injection in doses containing 0·375 g. of each, and 2, 4, and 6 hours after its administration an eosinophil count was carried out on the peripheral blood, together with estimation of the blood gentisate level. Apart from minor side-effects (giddiness), the drug was well tolerated.

In all cases there was a reduction in the eosinophil count resembling that seen after administration of ACTH. In ten patients the effect was compared with that of sodium gentisate, which caused an average reduction in eosinophil count of 13·5 per cent. compared with 38 per cent. when amidopyrine gentisate was given. Amidopyrine thus appeared to be the more active component part of the preparation. When the drug was given in the above dosage daily there was a definite reduction of pain in 90 per cent. of the patients with chronic rheumatism, within 1 or 2 days of starting treatment in cases of "rheumatic myalgia" and 10 to 12 days in cases of chronic polyarthritis. Acute rheumatism was less amenable, but even in these cases there was diminution of pain, temperature, and articular swelling after 4 or 5 days. The improvement in function was less obvious. In all cases in which the clinical response was satisfactory there was also some reduction in the erythrocyte sedimentation rate.

Cheapness and the possibility of prolonged administration without ill effect are claimed to be the main advantages of the drug, which was given in some cases after treatment had been started off with ACTH or cortisone. [It should be remembered, however, that prolonged administration of amidopyrine is not without

danger of agranulocytosis. There have been recent reports that similar effects may be obtained with buffered salicylates, the use of which would therefore be preferable.] *V. C. Medvei.*

New Form of Drug Therapy in the Treatment of Arthritis and Rheumatoid Conditions. NATENSHON, A. L. (1954). *Wis. med. J.*, **53**, 223. 5 refs.

The author has treated 200 unselected patients of various ages suffering from "arthritis in any form, acute or chronic; myositis; or any painful muscle condition, regardless of the cause" with "salimeph-C", a preparation containing 250 mg. salicylamide, 250 mg. mephenesin, and 15 mg. ascorbic acid in each tablet. It is stated that this combination is effective because mephenesin relaxes muscle spasm, salicylamide relieves pain without causing gastric irritation, and ascorbic acid compensates for depletion of vitamin C caused by salicylate.

Two tablets of salimeph-C were given 3 or 4 times a day after meals initially, to which dosage most patients responded within 3 days with loss of pain and stiffness and could then be kept symptom-free on 1 or 2 tablets daily. There were no side-effects, and it is claimed that results were "extremely good" in nearly all the patients, many who had been bedridden being able to get about without assistance. The treatment was effective in traumatic conditions (in which, however, other forms of treatment were also given), but did not relieve pain due to prolapse of an intervertebral disk or to calcified bursitis.

[There is no report of a control series, and no objective method of assessing improvement appears to have been used.] *F. Clifford Rose.*

Further Observations on the Metabolic Stimulating Effect of Salicylate. COCHRAN, J. B. (1954). *Brit. med. J.*, **1**, 733. 6 figs, 3 refs.

The author, working at the Gardiner Institute of Medicine, University of Glasgow, has previously shown (*Brit. med. J.*, 1952, **2**, 964; *Abstracts of World Medicine*, 1953, **13**, 185) that salicylate produces a marked increase in oxygen consumption in normal subjects and patients with subacute rheumatism. The present investigation was undertaken to determine the effect of salicylate and its isomers on the oxygen consumption of patients suffering from acute rheumatic fever.

Observations were made on three patients admitted to hospital with acute rheumatic fever, who were receiving 2 g. aspirin 4-hourly. The fall in temperature occurred in 24 to 48 hours and was accompanied by a rise in oxygen consumption, but the metabolic rate fell when aspirin was withdrawn. A fourth patient, being treated with sodium salicylate and bicarbonate, had a recrudescence of symptoms and there was a concurrent fall in his oxygen consumption on reduction of dosage or withdrawal of salicylate.

The effect of single doses of 3 g. salicylate or of aspirin were compared with single doses of 5 g. of the *para*- and *meta*-hydroxy isomers of salicylate on the same patient during convalescence. Sodium salicylate and aspirin caused a 12 per cent. and 11 per cent. increase respectively in oxygen consumption, while the isomers were without effect. Two other convalescent patients were given approximately 2 g. of the isomers 4-hourly over a 4-day period without significant increase in oxygen consumption. As the isomers are also known to be ineffective therapeutically, it is suggested that the therapeutic effect of salicylate must be related in some way to its metabolic effect. *Norval Taylor.*

Pulmonary Manifestations in the Diffuse Collagen Diseases. ELLMAN, P., and CUDKOWICZ, L. (1954). *Thorax*, **9**, 46. 12 figs, bibl.

The authors describe ten cases of diffuse collagen disease in which pulmonary manifestations occurred; the patients were seen at two London hospitals and at Dorking (Surrey) General Hospital. The series comprised three cases of scleroderma, two of disseminated lupus erythematosus, two of polyarteritis nodosa, and three of rheumatoid disease.

The presenting symptom of respiratory involvement in each case was dyspnoea, which in cases of polyarteritis nodosa was associated with wheezing and gave rise to a complaint of "asthma". In the cases of scleroderma, respiratory symptoms occurred late in the course of the disease. In one case, radiographs showed miliary mottling of the lungs associated with cardiac enlargement. In another, there was increasing dilatation of the pulmonary arteries, accompanied by pleural thickening and adhesions; while in the third case there was a basal fibrosis which later developed into sclerocystic disease of the lungs. One of the patients with disseminated lupus erythematosus showed bilateral basal fibrosis, and a unilateral effusion developed during an acute exacerbation in the 12th year of the disease; in the other a transient shadow in the right paracardiac region, at first thought to be an abscess and later assumed to be an area of "pneumonitis", was observed at the onset of the disease.

In both the cases of polyarteritis nodosa there was fine mottling in the upper zones, which resolved in one case. Respiratory symptoms occurred at the onset of the disease. Lastly, in the three cases of rheumatoid arthritis a pleural effusion, a transient paracardiac shadow with basal reticulation, and bilateral pleural effusion followed by basal pleural fibrosis were observed respectively.

In none of the cases studied were the lung lesions modified by treatment with ACTH or cortisone. The literature of pulmonary manifestations in collagen diseases is briefly reviewed. *Nigel Compston.*

Evaluation of the Ocular Findings in Lupus Erythematosus and their Aetiological Significance. (Die Bewertung der Augenbefunde für die Erkennung der Ätiologie beim Erythematodes.) ROHRSCHNEIDER, W., and EHRING, F. J. (1953). *Hautarzt.*, **4**, 451.

The authors describe the acute and chronic types of lupus erythematosus, the aetiology of which is still obscure. They disagree with those who think that the tubercle bacillus alone is a pre-disposing factor and assume that various other bacilli may contribute to its cause. *M. H. T. Yuille.*

Phenylbutazone Therapy in Joint Diseases. (La terapia con fenilbutazone nelle artropatie.) MANCINI, B., MELLONI, F., and PORRO, F. (1954). *Osped. maggiore*, **42**, 257. 2 figs, bibl.

Death from Hypersensitivity due to Phenylbutazone. O'BRIEN, D. J., and STOREY, G. (1954). *Brit. med. J.*, **1**, 792. 4 figs, 19 refs.

Stevens-Johnson Syndrome and Granulocytopenia after Phenylbutazone. STEEL, S. J., and MOFFATT, J. L. (1954). *Brit. med. J.*, **1**, 795. 5 refs.

Palindromic Rheumatism with special reference to the Therapeutic Results with Gold and ACTH. LEWITUS, Z. (1954). *Rheumatism*, **10**, 70. 6 refs.

Critical Examination of Hyaluronidase Theories in Rheumatic Diseases. (Zur Kritik der Hyaluronidase-Theorien bei rheumatischen Erkrankungen.) ROSSING, P. (1954). *Ärztl. Wschr.*, **9**, 544. Bibl.

Treatment of Chronic Joint Disease with a Derivative of *Colchicum autumnale*. (Trattamento delle artropatie croniche con un derivato del *Colchicum autumnale*.) RIZZENTE, S. (1954). *Minerva med. (Torino)*, **45**, 1784. 2 figs, 8 refs.

Experimental Investigations on Percutaneous Salicylate Therapy. (Experimentelle Untersuchungen zur perkutanen Salizyl-Therapie.) FIEBIG, W. (1954). *Z. Rheumaforsch.*, **13**, 151. 4 figs, 13 refs.

Further Studies on Compounds reducing Synovial Membrane Permeability. BIANCHI, C. (1954). *Brit. J. Pharmacol.*, **9**, 166. 14 refs.

Diagnosis of Psychogenic Rheumatism. (Diagnóstico de lo psicógeno en reumátología.) MONTSERRAT, S. (1954). *Rev. esp. Reum.*, **5**, 307.

Rheumatic Syndromes with Psychogenic Elements. (Síndromes reumáticos con revestimiento psicógeno.) MONTSERRAT, S., and SANS SOLÁ, L. (1954). *Rev. esp. Reum.*, **5**, 312.

Polyarthritis in Rubella. LEWIS, G. W. (1954). *Rheumatism*, **10**, 66. 14 refs.

Microbe Therapy of Rheumatic Polyarthritis. KONO, M., YOSHIDA, T., NAKAYAMA, T., ONO, M., SUGIHARA, H., SOMEYA, K., and ISHIBASHI, H. (1953). *Yokohama med. Bull.*, **4**, 304. 5 figs, 25 refs.

Radiological Study of the Femoral Head in the Aged Subject. (Étude radiologique de la tête fémorale du sujet agé.) JACQUELINE, F., and VERAGUTH, P. (1954). *Rev. Rhum.*, **21**, 237. 6 figs, 4 refs.

Brucellosis and Rheumatism. (Brucelosis Y Reumatismo.) TARNOPOLSKY, S., GOOBAR, J. P., and DOUTHAT, A. (1954). *Pren. med. argent.*, **41**, 1911.

Trochanteritis. (La trochantérite.) FRANÇON, F. (1954). *Rev. Rhum.*, **21**, 230. 1 fig.

Relationship between Rheumatoid Arthritis and Osteo-Arthritis of the Spine. (Über den Zusammenhang zwischen primär chronischer Polyarthritis und Spondylosis deformans.) TREICHLER, J. (1954). *Z. Reumaforsch.*, **14**, 129. 3 refs.

Benign Backache in the Adult. (Les dorsalgies bénignes de l'adulte.) ARLET, J. (1954). *Rev. Rhum.*, **21**, 303.

Rheumatic Abdominal Lymphadenitis. (Linfadenitis abdominal reumatica.) BARCELÓ, H. (1954). *Arch. argent. Reum.*, **17**, 51, 57. 1 fig., 9 refs.

Research Activities in Rheumatic Diseases. BUNIM, J. J. (1954). *Publ. Hlth Rep. (Wash.)*, **69**, 437. 2 figs.

Disk Syndrome

Protruded Lumbar Intervertebral Disks in Children. WEBB, J. H., SVIEN, H. J., and KENNEDY, R. L. J. (1954). *J. Amer. med. Ass.*, **154**, 1153. 2 figs, 4 refs.

In a review of the records of 6,500 patients with protruded intervertebral disk in the lumbar region treated surgically at the Mayo Clinic between 1942 and 1952, the authors found that 25 patients were under 18 and five (0·077 per cent.) were aged 12 to 15 years.

It is these latter five patients, four girls and one boy, who are here described. A history of significant trauma was obtained in three of the cases. The symptoms, which had persisted for periods of 3 to 12 months in spite of conservative treatment, consisted predominantly of pain in the lower part of the back, hip, and ankle; there was sciatic pain, bilateral in three cases and left-sided in two; numbness in the legs (three cases), and weakness in one leg (two cases). Among the signs were: limitation of movement of the lumbar spine with, in some cases, a certain degree of scoliosis, spasm of the paravertebral muscles, pain in the hip on flexing the neck, tenderness on percussion over the lower lumbar or lumbo-sacral interspaces, limitation in raising the extended leg on one or both sides, and a diminished ankle reflex. Myelography was performed in all cases and revealed protrusion of an intervertebral disk in the fourth lumbar interspace in four cases (one being lateral and three central) and a midline lumbo-sacral protrusion only in the fifth case.

All protrusions were removed at operation, at which swelling and stretching of nerve roots were noted in some cases. In one case bilateral bone grafts were inserted from the 3rd lumbar vertebra to the 2nd sacral segment. The results are known to be good in four cases followed up for periods up to 8 years and the fifth patient was free of pain when last seen on discharge. The symptoms and the clinical and pathological findings of protruded intervertebral disk are similar in adults and children, and although the lesion is rare in children, the possibility of its occurrence should be borne in mind. *V. Reade.*

Pain associated with Cervical Spondylosis. TAYLOR, A. R. (1954). *Rheumatism*, **10**, 52. 25 refs.

Gout

Effect of Intravenous Colchicine on Acute Gout. DAVIS, J. S., and BARTFELD, H. (1954). *Amer. J. Med.*, **16**, 218.

In the past acute gout was frequently treated parenterally by injecting intravenously the contents of a 20-ml. ampoule, made up of 0·65 mg. colchicine, 1 g. sodium salicylate, and 1 g. sodium iodide. Side-effects, such as intestinal haemorrhage, were not uncommon. As these were ascribed to salicylates and iodides, the authors, in an investigation at St. Luke's Hospital, New York, decided to omit these substances and prepare a solution containing 0·65 mg. (1/100 gr.) of colchicine in distilled water in 1- and 2-ml. ampoules. This modified preparation was given to sixteen patients suffering from acute attacks of gout. In some cases up to eight injections were required to bring the attack under complete control, but in four instances the attack was aborted by a single injection, pain and swelling often beginning to subside within 5 to 15 minutes. *D. Preiskel.*

Primary and Secondary Gout. GUTMAN, A. B. (1953). *Ann. intern. Med.*, **39**, 1062. 1 fig., bibl.

The author's definition of primary gout as an inborn error of metabolism and secondary gout as an accompaniment of certain disease processes, such as polycythaemia, leukaemia, and haemolytic anaemia, is in accordance with current medical thought. The major pathways of purine metabolism are:

(1) the biosynthesis of purines and purine derivatives from simple carbon and nitrogen compounds;
(2) the degradation of endogenous nucleic acids;
(3) the degradation of ingested preformed nucleoproteins and purines.

The author points out that the first of these is mainly involved in primary gout and the second in secondary gout, while the third factor may affect the course of both types. The possible role of the kidney is discussed, and the author shows that there is no clear evidence for a specific renal defect in either primary or secondary gout.

The treatment of the primary and secondary forms is essentially the same. ACTH (corticotrophin) is considered the most effective therapeutic agent for the acute attack, an initial dose of 50 to 200 mg. followed by 50 to 100 mg. daily for several days, or a single dose of 100 mg. ACTH gel, being recommended. Colchicine and phenylbutazone are also recommended, but neither is a perfect therapeutic agent and the toxic effects of the former may be serious. For the chronic case the importance of diet is stressed, proteins being limited to 50 to 75 g. daily and so far as possible taken in the form of milk; fat intake should also be strictly curtailed. "Benemid" (probenicid) in a dosage of 0·5 to 3 g. daily increases urate clearance and is considered to be a valuable agent in the treatment of chronic gout. No distinction is drawn between the therapeutic management of primary and secondary gout, save that in secondary gout steps must be taken to deal with the underlying disease. *R. E. Tunbridge.*

Phenylbutazone (Butazolidin) in Gout. KUZELL, W. C., SCHAFFARZICK, R. W., NAUGLER, W. E., GAUDIN, G., MANKLE, E. A., and BROWN, B. (1954). *Amer. J. Med.*, **16**, 212. 4 figs, 13 refs.

In an attempt to evaluate the therapeutic efficacy of phenylbutazone 200 patients (156 males and 44 postmenopausal females) suffering from acute gout and/or chronic gouty arthritis and treated with this drug were studied at Stanford University School of Medicine, San Francisco, in the 30 months November, 1950, to May, 1953. During the first 8 months "Irgapyrin" (containing equal parts of phenylbutazone and aminopyrin) was used. For the most part phenylbutazone was given orally; when injected intramuscularly it was given in the form of its sodium salt (20 per cent. solution) and occasionally combined with a local analgesic. A series of 408 cases of musculo-skeletal disorders other than gout, also treated with phenylbutazone, were used as controls, the serum uric acid level being estimated before and after treatment.

In acute gout an injection of 1 mg. phenylbutazone daily for 1 to 3 days sufficed to relieve symptoms. The extent of such relief was greater than that previously experienced with colchicine and/or hormone therapy, and was occasionally noted in less than one hour. Small oral doses (200 to 400 mg. daily) also caused rapid subsidence of symptoms. The attack rate among patients receiving a small daily dose (200 to 600 mg.) was greatly reduced. Those with acute gout responded better than those with chronic gouty arthritis, and in general males did better than females. The serum uric acid level in those receiving a maintenance dose of 100 mg. daily did not appear to be decreased, but the "uric acid pool" was not estimated; tophi were not influenced in any way. Toxic effects were slight and necessitated discontinuation of treatment in 7 per cent. of gouty cases; in the non-gouty patients the drug had to be stopped in 22 per cent. It was also noted that the relief of pain in the non-gouty group was less in patients with a raised serum uric acid level than in those in which it was normal, thus suggesting that the characteristic lowering of serum uric acid level by phenylbutazone was not the most important pharmacological action of the drug.

Though phenylbutazone appears to have a specific effect in gout, its mode of action has still to be determined. The authors have been unable to confirm the alleged increased urinary excretion of uric acid, and they explain how errors in calculation are apt to arise. Possibly, they state, the drug acts by delaying the degradation of nuclein; it may also affect enzymes concerned in the metabolism of purines. In a concentration of 1 : 5,000 phenylbutazone will completely inhibit the growth of yeast, and this inhibition seems to be unaffected by the addition of a variety of substances, such as ascorbic acid, glucose, and vitamin-B complex. On the other hand, sodium bicarbonate in a concentration of 1 : 1,000 decreased this inhibitory effect by 70 per cent.

D. Preiskel.

Sodium Salicylate and Gout. JENNINGS, G. H. (1954). *Rheumatism*, **10**, 58. 4 figs, 31 refs.

General Pathology

Prothrombin Time in Rheumatic Fever. (Le temps de prothrimbine dans le rhumatisme articulaire aigu.) STERNE, J. (1954). *Arch. Mal. Coeur*, **47**, 257.

This study, carried out on 54 cases at the Maurice Gaud Hospital, Casablanca, is claimed to be the first systematic investigation of the changes in prothrombin time in rheumatic fever. All samples were collected by the same observer and estimations were made by Quick's method. The results were divided into three categories:

(I) normal, when the reading was 80 per cent. or above;
(II) moderately lowered (50 to 75 per cent.);
(III) considerably lowered, when the figure was 50 per cent. of normal or below.

Of the 54 patients investigated, twelve belonged to Category I, nineteen to Category II, and 23 to Category III. In fifteen patients without cardiac involvement, the prothrombin time was normal in six, reduced in three, and low in six, but in the 39 patients with cardiac involvement it was normal in only six, reduced in sixteen, and considerably lowered in seventeen.

Prothrombin time and erythrocyte sedimentation rate (E.S.R.) do not necessarily run parallel; a reduction in the former was found to be a better guide to a coming relapse in a number of cases. An accelerated E.S.R. may co-exist with a normal prothrombin time but the latter may be 50 per cent. of normal while the E.S.R. is 3 to 10 mm. in the first hour (Westergren). The value of prothrombin time estimation is greater than that of the E.S.R. in that it is more specific in acute arthritis. Prothrombin time is decreased in rheumatic fever, but not in rheumatoid arthritis, and thus has diagnostic importance; the only other type of arthritis in which it is decreased is acute gonococcal arthritis. In spite of the decreased prothrombin time in rheumatic fever there is marked tolerance to heparin and this also is said to be of diagnostic significance. *D. Preiskel.*

Sternoclavicular Articulation in Rheumatic Diseases. SOKOLOFF, L., and GLEASON, I. O. (1954). *Amer. J. clin. Path.*, **24**, 406. 7 figs, 12 refs.

The sternoclavicular joint, examined *post mortem*, was found to be affected by "rheumatic" disorders more frequently and more severely than is generally appreciated. The material was obtained from Bellevue Hospital, New York, from cases of rheumatoid arthritis, gout, infective arthritis, lupus erythematosus, and acute rheumatic disease. For comparison the appearance of the normal sternoclavicular joint and the degenerative changes occurring with age are described. [The number of cases was small, but the illustrations are good proof of the value of examination of this accessible material.] *A. C. Lendrum.*

Pathogenesis of Non-Specific and Rheumatic Bursitis. (Zur Pathogenese der unspezifischen und rheumatischen Schleimbeutelentzundüngen.) BÖHMIG, R. (1954). *Zbl. allg. Path. path. Anat.*, **91**, 245. 3 figs, 16 refs.

Examination at the City Pathological Institute, Karlsruhe, of thirty excised bursae, 21 of which were diagnosed as examples of non-specific and nine of rheumatic bursitis, showed the following changes.

(1) *Serous inflammation.*—This lesion was most pronounced in acute bursitis, and is therefore seldom examined histologically. The protein-containing exudate occurs under the endothelial lining of the bursa, but may also separate the atrophied collagen fibres below it. These fibres may show small groups of cells with pyknotic nuclei, loss of chromatin and staining, and even reduction of the nuclei to nuclear shadows.

(2) *Fibrinous inflammation.*—This was found to be present in all subacute and subchronic cases. The fibrin is laid down in layers immediately under the endothelial lining of the bursa and between the deeper collagen fibres. Villous projections develop from the endothelial surface into the lumen; they are covered with endothelium and filled with hyalinized material, larger or smaller amounts of fibrin, and elastic fibres or relics of them.

(3) *Haemorrhages and cellular infiltration.*—In this series both these findings were rare. When cellular infiltration occurs it is mainly into the middle and outer walls of the bursae.

(4) *Formation of new vessels.*—The author distinguishes between the vascular structures developing from arterioles in the middle wall and the new capillaries which develop in the inner wall, often in association with villous projections.

(5) *Histiocytic proliferation.*—This appeared to occur during fibrinous inflammation, and developed either in the subendothelial layer (particularly in the fibrinous centres of the villi) or in the intercollagenous bands of fibrin. Palisading of histiocytes may occur to replace the endothelium, in whole or in part, or to cover the outer layers of fibrin; it is always associated with formation of new capillaries.

The author considers that the association of interstitial fibrinous inflammation, histiocytic proliferation, and formation of new capillaries is characteristic of rheumatism, and compares bursitis fibrinosa simplex (which does not possess all these characters) with non-specific fibrinous endocarditis, and also rheumatic fibrinous bursitis with rheumatic endocarditis. *C. L. Oakley.*

Gaucher's Disease in 29 Cases: Haematological Complications and Effect of Splenectomy. MEDOFF, A. S., and BAYRD, E. D. (1954). *Ann. intern. Med.*, **40**, 481. 12 refs.

The authors review all the proved cases of Gaucher's disease, 29 in number, seen at the Mayo Clinic during 1950. The clinical features are described in detail. Of special interest was the age at onset of symptoms; when first seen, three of the patients were under 9 years of age, eight were 10 to 19 years of age, three were 20 to 29 years, six were 30 to 39 years, six were 40 to 49, and three were over 50. The sex distribution was approximately equal.

Splenomegaly and anaemia were almost constant findings, and splenectomy was carried out in fifteen of the cases for the relief of abdominal distension or hypersplenism. [A Table setting out the haematological findings indicates that there was leukopenia with a reduced platelet count in five of the fifteen cases, but there is no reference to the results of sternal marrow biopsy in the latter cases.] Splenectomy had no deleterious

effect on the course of the disease. Two patients died in the post-operative period, and of the remaining thirteen, six were alive 11 to 20 years after the operation. The authors note that of the fourteen patients treated conservatively, one was alive 12 years after attending the clinic and two were alive 14 years afterwards.

The follow-up investigation for the whole series was not complete, so that the findings could not be subjected to statistical analysis. *R. E. Tunbridge.*

Collagen Fibrillar Structure of the Articular Cartilage of the Knees studied with the Aid of Polarized Light. (Estructuración fibrilar colágena del cartílago articular de la rodilla, con la ayuda de la luz polarizada.) GUIRAO PÉREZ, M. (1954). *Rev. esp. Reum.*, **5**, 278. (received June, 1954). 19 figs.

Writing from the University of Granada, the author describes a study made at the Karolinska Institute, Stockholm, of the direction of collagen fibres in the articular cartilage of the knee-joint, the material consisting of 34 fresh post-mortem foetal and adult joints. His method consists in filling the cavities with indian ink and observing prepared sections by means of polarized light. The technique is given in detail. He describes five zones of fibres: vertical, oblique, horizontal, perpendicular, and superficial, and attempts to correlate their direction with the mechanical function of the joint. His conclusions are supported and illustrated by photomicrographs, diagrams, and drawings, and the literature is discussed in detail at considerable length. *L. Michaelis.*

Capillary Permeability. Rheumatism and Cortisone. (Permeabilità capillare. Reumatismo e cortisone.) SCALABRINO, R., and PASQUARIELLO, G. (1954). *Reumatismo*, **6**, 69. 4 figs, bibl.

Investigations on capillary permeability in eleven rheumatic and seven non-rheumatic patients are reported. The anatomical, functional, chemical, and enzymatic characteristics of capillaries are discussed at length. The theory that rheumatism, in the broad sense, involves a disturbance of capillary permeability is examined, and reference is made to reports of the effect on the capillaries of cortisone and ACTH (corticotrophin). The Landis test was used in the authors' investigations. This consists in determining the amount of water and protein lost from the blood over a period of 30 minutes in a limb compressed proximally by a tourniquet at a pressure of 80 mm. Hg, as calculated by comparison of the haemocrit values and protein content of venous blood taken from the compressed limb and from that of the opposite side. In normal subjects the average loss is stated to be 18·7 ml. water and 0·22 g. protein per 100 ml. blood.

In the cases of acute and chronic rheumatism investigated the average loss of water was 31·9 ml. and of protein 1·48 gr. per 100 ml. before treatment, while in seven cases of non-rheumatic disease (four of liver disease, one of chorea, one of Hodgkin's disease, and one of asthma) the average figures were 24·9 ml. and 0·69 g. respectively. Cortisone was then given for 2 to 5 days, the total dosage being 150 to 850 mg. The test was repeated on one or two occasions 1 to 5 days after the omission of cortisone, mainly on the 2nd or 4th day. It is stated that cortisone produced a constant, immediate, and considerable diminution in capillary permeability in rheumatic subjects and, to a lesser degree, in non-rheumatic patients. [The figures do not bear out completely: water loss increased in three of five cases examined on the second day. Loss of protein, however, diminished in all cases, irrespective of any increase in water loss.] The implications of the results claimed are discussed at some length. *W. A. Bourne.*

Erythrocyte Sedimentation Rate and the Plasma Viscosity. EASTHAM, R. D. (1954). *J. clin. Path.*, **7**, 164. 4 figs, 14 refs.

Relationship between Plasma Mucoproteins and Protein Sugar in Patients with Rheumatoid Arthritis receiving Cortisone. BADIN, J., and GLYN, J. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **86**, 150. 1 fig., 8 refs.

Hyaluronidase-Haemoglobin Dispersion Test in the Acute and Chronic Rheumatic States of Childhood. (Le test de dispersion hyaluronidase-hémoglobine dans les états rhumatismaux aigus et chroniques de l'enfance.) MAURICE, P. (1954). *Acta paediat. belg.*, **8**, 60. 8 figs, 16 refs.

Use of the Agglutination of Sensitized Sheep's Erythrocytes in the Diagnosis of Rheumatoid Arthritis. (Utilidad en el diagnostico de la artritis reumatoide de la reaccion de aglutinacion para los hematies sensibilizados de carnero.) PUIG LEAL, J., ALÉS REINLEIN, J. M., and FERNÁNDEZ DEL VALLADO, P. (1954). *Rev. clin. esp.*, **53**, 28. 10 refs.

Researches into the Nature of the Waaler-Rose Reaction. (Ricerche sulla natura della reazione di Waaler-Rose.) DANEO, V., and EINAUDI, G. (1954). *Reumatismo*, **6**, 252. 10 refs.

ACTH, Cortisone, and Other Steroids

Intra-articular Hydrocortisone Acetate in Rheumatic Disorders. BORNSTEIN, J., SILVER, M., NEUSTADT, D. H., BERKOWITZ, S., and STEINBROCKER, O. (1954). *Geriatrics*, **9**, 205. 7 refs.

In this paper from the Lenox Hill Hospital and the Hospital for Joint Diseases, New York City, are recorded the results in 88 patients with rheumatic disorders who received a total of 280 local injections of hydrocortisone acetate. Their ages ranged from 5 to 75 years, the largest number being in the 4th, 5th, and 6th decades. Of the 88 patients, 35 had rheumatoid arthritis and 25 osteo-arthritis; the remainder had miscellaneous conditions. The dose was 1 or 2 ml. at intervals varying from a few days to several weeks, according to the rate of return of symptoms.

The results were good in rheumatoid arthritis, 83 per cent. of the joints injected showing some benefit. In osteo-arthritis improvement was obtained only in 48 per

cent., and was purely subjective in the majority of these. Especially good responses were observed in the seven cases of tenosynovitis of the fingers, five showing complete resolution and the other two "major improvement". Four out of five patients with acute calcific tendonitis also benefited greatly after injections into the supraspinatus tendon. The duration of effect was very variable, but in the majority of cases reinjection was needed at intervals of 1 to 2 weeks.

The authors consider that one of the chief advantages of local hydrocortisone therapy is avoidance of systemic hormonal effects, especially in patients with rheumatoid arthritis and osteo-arthritis, who tend to belong to the older age groups, in which there is a liability to such complications as heart failure, mental disturbances, and pathological fractures. *K. C. Robinson.*

Potentiation of Cortisone by Glycyrrhetinic Acid. HART, F. D., and LEONARD, J. C. (1954). *Lancet*, **1**, 804. 1 fig., 3 refs.

In view of the restricted supply of cortisone as yet available, any drug which might intensify its therapeutic action is worth investigation.

Work reported from Holland and elsewhere having suggested that liquorice and glycyrrhetinic acid might have such an effect, the present authors carried out tests at the Westminster Hospital, London, on eleven patients with rheumatoid arthritis under carefully controlled conditions for 5 to 7 days. The results of this investigation were discouraging, and it is concluded that if there is any potentiation of cortisone by glycyrrhetinic acid it is too slight and inconstant to be of value in the treatment of rheumatoid arthritis. *Oswald Savage.*

Treatment of Acute Disseminated Lupus Erythematosus with Corticotropin and Cortisone. SOFFER, L. J., ELSTER, S. K., and HAMERMAN, D. J. (1954). *Arch. intern. Med.*, **93**, 503. 2 figs, 11 refs.

A study was made at the Mount Sinai Hospital, New York, of the effects of treatment with cortisone or ACTH (corticotrophin) on 32 patients with acute systemic lupus erythematosus, 26 of whom were females and six males. The patients' ages varied from 11 to 60 years, but the incidence of the disease was highest during the second, third, and fourth decades. Most of the patients had been ill for 6 months to 2 years before admission, but three had had the disease for more than 5 years. During this period spontaneous remissions had occurred in most of the patients, lasting between 2 weeks and many months. Joint pains, with or without demonstrable abnormalities of the joints, were the initial symptoms in more than half the cases, and fever of varying degree was present in almost all. Other manifestations included loss of weight, a characteristic facial eruption, shallow, ulcerated lesions of the mucous membrane, generalized lymphadenopathy (the nodes being discrete, moderately enlarged, and not tender), enlargement of the liver and spleen, pericarditis (with or without effusion), and hypertension, which was almost always associated with renal damage. Most of the patients had either a normal leucocyte count or a leucopenia and a varying degree of anaemia. L.E. cells were readily found in the peripheral blood in all cases, so that examination of the sternal bone marrow was generally unnecessary. False positive reactions to the serological tests for syphilis were met at one time or another in more than one-third of the series.

Initially, 100 mg. ACTH a day was given intramuscularly in four doses, but acutely ill patients received a slow intravenous infusion of 20 to 40 mg. dissolved in 500 to 1,000 ml. 5 per cent. dextrose solution over an 8-hour period. The daily dosage of cortisone varied from 200 to 400 mg., but was occasionally as much as 800 mg., given in four doses. After the acute manifestations had subsided the daily maintenance dose of ACTH required varied from 25 to 75 mg., and of cortisone from 50 to 100 mg. In some cases it was possible to stop treatment entirely for variable periods. The hypertension, hepatomegaly, and splenomegaly responded either poorly or not at all to the treatment, but the fever, joint pains, rash, and mucosal lesions subsided. In all cases, however, L.E. cells continued to be found in the peripheral blood, and in only a small number was there any significant improvement in renal function. Complications of the treatment included rounding of face, psychiatric abnormalities (euphoria, depression, or paranoid trends), hypertension, oedema, infections, acne, hirsutism, and metabolic alkalosis. To prevent the development of alkalosis 2 to 6 g. potassium chloride was given daily either orally or parentally as a routine. Most of the side-effects were reversible when the dosage of hormone was reduced or treatment stopped.

After periods of observation ranging from 1 to 40 months, 23 of the 32 patients had survived and were reasonably well, eight having been in a state of remission without treatment for 2 to 30 months and the remaining fifteen receiving maintenance treatment. Nine patients had died, six from progressive renal failure, one from status epilepticus, one from a disseminated fungus infection, and one because of inadequate therapy.

E. W. Prosser Thomas.

Oral Cortisone Treatment of Hypopituitarism. SHEEHAN, H. L., and SUMMERS, V. K. (1954). *Brit. med. J.*, **1**, 723. 22 refs.

The authors report the results obtained at Walton Hospital, Liverpool, with small doses of cortisone by mouth in the treatment of hypopituitarism in four patients (three women and one man) who were maintained for periods up to 2 years on a dose of 12·5 mg. daily. Doses up to 37·5 mg. daily were given at the beginning of treatment, and rapidly produced a normal capillary flush in the face, a return of axillary secretion, a feeling of well-being, and increased appetite, but insomnia occurred in two cases. When the dose was reduced the insomnia disappeared and the improvement was maintained.

The growth of body hair increased in two cases, though it never became normal. The treatment had no effect on amenorrhoea. In the man there was a return of libido and coitus became possible without, however, resulting in an emission. In general, there was a gain in weight, an improvement in anaemia, and an increase in

the 24-hour urinary volume and in the diuresis following the ingestion of water.

The urinary 17-ketosteroid excretion initially ranged from 0·2 to 1 mg. and increased under treatment to a level of 2·1 to 2·8 mg. per day. *G. A. Smart.*

Female Pseudohermaphroditism: Response to Cortisone Therapy. VINES, R., and DODS, L. (1954). *Aust. Ann. Med.*, **3**, 5. 15 figs, 13 refs.

The authors describe from the Royal Alexandra Hospital for Children, Sydney, the results of the treatment with cortisone of six cases of female pseudohermaphroditism due to adrenocortical hyperplasia. Four of the patients were aged 16, 9, 7, and 5 years respectively, the other two being infants aged 10 weeks when treatment was begun. The four older girls were given cortisone by mouth in large doses, varying from a total of 25 to 150 mg. daily. They all showed marked clinical and psychological improvement. The first changes to become apparent were diminution in the acne and development of the breasts, the latter beginning within 2 to 6 months of the start of treatment in all four patients and progressing steadily thereafter, while the two eldest girls began to menstruate in 5 to 7 months. The level of 17-ketosteroid excretion was high in all four cases, but fell to levels which were approximately normal for girls of a corresponding stage of development, rather than for girls of the same chronological age.

The two infants were treated because of emaciation, vomiting, and marked enlargement of the clitoris. One responded satisfactorily to cortisone by mouth in doses which varied between 7·5 and 30 mg. daily; but the other continued to show signs of severe adrenocortical insufficiency and was treated by intramuscular injection of 15 mg. cortisone on alternate days and 8 mg. deoxycortone daily, together with an additional 4 g. salt daily. Side-effects such as moon-face and increase of weight were not severe, and in no case did virilism develop. It is suggested that cortisone therapy should be started by the parenteral route, since reduction of 17-ketosteroid excretion is thus more reliably achieved and smaller doses of the hormone are required by this method.

The results in five of these cases are regarded as highly satisfactory, particularly in their psychological effects on the older girls, but how long cortisone therapy will have to be continued is not yet known. *A. C. Crooke.*

Further Studies on the Treatment of Congenital Adrenal Hyperplasia with Cortisone. V. Effects of Cortisone Therapy on Testicular Development. WILKINS, L., and CARA, J. (1954). *J. clin. Endocr.*, **14**, 287. 7 figs, 13 refs.

Previous work has shown that after cortisone therapy female pseudohermaphrodites suffering from adrenal hyperplasia develop female secondary characteristics and may start menstruation if the patients are more than 8 years old. In younger patients the results of treatment on sexual development are slight or *nil*. The onset of adolescent development depends on somatic (bone) age and not on chronological age.

In the present paper from Johns Hopkins Hospital, Baltimore, similar findings in boys with macrogenitosomia praecox are recorded. Of the seven boys of chronological age of 3 to 8 but whose bone age was 9 to 14, all had high rates of 17-ketosteroid excretion (8 to 40 mg. per day) and equivalent development of secondary sex characteristics. The testes, however, in all of them were of pre-adolescent size and biopsy in six cases showed undifferentiated cells in the tubules, with spermatogonia, few or no spermatocytes and Sertoli cells, and no Leydig cells. Treatment with cortisone reduced the 17-ketosteroid excretion to below 4·5 mg. per day in six of the boys and to 7 mg. in the seventh. The testes did not enlarge and there was no change in testicular structure in the three boys with bone ages of 9 to 10½ years, but some enlargement and increased seminiferous differentiation occurred in a boy with a bone age of 11 years, though no Leydig cells appeared. Full testicular maturation with enlargement to adult size, spermatogenesis, and Leydig-cell development occurred in the remaining three boys whose bone ages were 11 to 14 years. There was increased virilization in these cases but not in those with no testicular changes. One of the patients had a nodule of aberrant adrenal (reticular zone) tissue in one testis.

The authors suggest a probable explanation of the mode of action of cortisone. The excess of oestrogen and androgen secreted by the hyperplastic adrenal inhibits pituitary gonadotrophin secretion, although the androgen may cause some degree of seminiferous development. Cortisone, by suppressing the adrenal overactivity, releases the inhibited secretion of gonadotrophin. Cortisone has no direct effect on the testes in patients with other disorders. It also appears that somatic development must have reached a certain stage (in the present cases a bone age of 11 to 13 years) before the testes become responsive to gonadotrophin. Corroborative evidence for this was provided by the cases of two boys from whom virilizing adrenal tumours were removed; in both the 17-ketosteroid excretion was markedly reduced, but no change in testicular size or structure occurred in one boy whose bone age was 5½ years, while testicular enlargement and maturation occurred in the other, whose bone age was 12 years.

Peter C. Williams.

Anaphylactoid Reaction from ACTH. Report of a Case. SWIFT, S. (1954). *Ann. Allergy*, **12**, 172. 5 refs.

The case is reported of an asthmatic who had received ACTH (corticotrophin) on twelve occasions within 12 to 18 months. One hour after a further injection she developed giant urticaria, nausea, diarrhoea, and severe dyspnoea. These symptoms subsided gradually. Subsequent skin tests with aqueous ACTH and with ACTH gel of different brands gave positive results, as also did tests with anterior pituitary extract, whereas negative results were obtained with posterior pituitary extract and with pork and beef extracts. The results of passive transfer tests were also positive. *H. Herxheimer.*

Severe Asthma treated with Corticotrophin. BALL, K. (1954). *Lancet*, **1**, 1162. 2 figs, 1 ref.

A controlled investigation of the value of corticotrophin in severe asthma was carried out at the Central

Middlesex Hospital, London. Only patients whose asthma had persisted for at least 3 months without 2 weeks' complete remission in that time were included. Of the thirteen patients, six received injections of corticotrophin and seven injections of saline, but at the time of the trial the identity of the patients receiving the two different treatments was not known. Of the six patients given corticotrophin intramuscularly to a total dose of 1 g. in 12 days, five improved, compared with two of the seven given saline, though one of the latter group subsequently responded to corticotrophin. There was a relapse within 28 days in three of the patients who responded to corticotrophin, but two of these benefited later from a second course. Definite amelioration of symptoms over periods varying from 1 to 13 months (average 6 months) was noted in twelve patients in status asthmaticus who were given a maintenance dose of 20 to 80 mg. daily. These results, and observations on patients given cortisone, are considered to prove that these drugs are beneficial, and indeed essential, in cases of status asthmaticus. Complications such as water retention were rare. *K. Gurling.*

Infantile Eczema treated with Oral Cortisone. A Clinical Report. SOLOMONS, B. (1954). *Brit. med. J.*, **1**, 1190. 5 refs.

Experience of the administration of cortisone to infants and young children suffering from severe atopic eczema is reported. The drug was given by mouth in a dosage of 75 mg. daily to twelve patients and 87·5 mg. daily to three others for periods of 1 to 3 months. A lasting and satisfactory response appeared to be obtained in three children; in six there was some improvement and in six the treatment was without effect. Some improvement in the general condition and well-being was observed in the majority of the children. Toxic effects were not important. *Winston Turner.*

Corticotropin (ACTH) in Severe Tetanus. LEWIS, R. A., SATOSKAR, R. S., JOAG, G. G., DAVE, B. T., and PATEL, J. C. (1954). *Indian J. med. Sci.*, **8**, 1. 11 figs, 18 refs.

Because of previous experience of the beneficial effect of adrenal hormone therapy in convulsions induced in animals by exposure to reduced oxygen tension the authors were encouraged to study its effect on tetanus. From cases of tetanus admitted to the King Edward Memorial Hospital, Bombay, only the most severe were selected for study, at least four of the following being required to be present:

(A) trismus;
(B) convulsions while under observation;
(C) incubation period of 7 days or less;
(D) onset period of 48 hours or less;
(E) rectal temperature of 100° F. (37·8° C.) or more within 24 hrs of admission or 48 hrs of onset.

Treatment with intravenous ACTH (corticotrophin) was given in alternate cases satisfying these criteria, each patient receiving 20 to 25 mg. ACTH dissolved in 2 l. 5 per cent. glucose solution 8- or 10-hrly at first, the last five patients out of ten treated receiving the same dose 2-hrly at the beginning of treatment. The duration of treatment varied from 4 to 8 days and the total dose of ACTH from 80 to 160 mg. The ten control subjects were given intravenous injections of 5 per cent. glucose, and all the patients received routine treatment, such as tetanus antitoxin, penicillin, and wound toilet.

The most striking effect of ACTH was on the fever, the temperature in treated cases being sometimes normal by the third day, especially when more frequent doses were given at the beginning. The respiration and pulse rates were also reduced. The part played by ACTH in the relief of trismus and the reduction of convulsions was more difficult to evaluate, but some relief was usually obtained after the second day of treatment and in several cases there was a return or an aggravation of the spasms when the dose of ACTH was reduced or omitted. An attempt was made to follow the course of the eosinophil count, but this was found to be depressed by the tetanus toxin, reaching zero by the second day in all fatal cases but one, and, in the survivors, tending to rise towards normal during the phase of recovery. It was noted, however, that even when the eosinophil count was zero a beneficial clinical effect was still obtained by giving ACTH, suggesting that although in tetanus there is a great outpouring of adrenal hormones, even more can be elicited by treatment with ACTH. Toxic effects from the ACTH were not marked as the drug was not administered over long periods.

Among the ten patients treated with ACTH there were four deaths, and among the ten control subjects seven. Although the series is too small to have statistical value, it is considered significant that none of the patients receiving ACTH succumbed after completing 48 hours of treatment. *J. V. Armstrong.*

Preliminary Report on the Prolonged Intermittent Administration of ACTH in the Treatment of Lipoid Nephrosis. (Preliminari risultanze sul trattamento ciclico prolungato della nefrosi lipoidea con ACTH.) CHELI, E., and MARINI, C. (1954). *Clin. pediat.* (*Bologna*), **36**, 83. 4 figs, bibl.

From the Paediatric Clinic of the University of Modena are reported the cases of two children, aged 5 and 4½ years respectively, suffering from severe lipoid nephrosis of long standing. Practically all known therapeutic measures had been tried, including the administration of thyroid extract, adenosine phosphoric acid, and isoniazid, plasma transfusion, deep *x*-ray therapy to the pituitary gland, and ultrashort-wave therapy to the adrenal glands, all of which had failed to stop the progress of the disease, proteinuria, oliguria, oedema, hypoproteinaemia, and hypercholesterolaemia, remaining generally unaffected.

Finally, the effect of ACTH (corticotrophin) was tried, a total dosage of 1,550 mg. being given in 9 weeks; three doses totalling 50 mg. were injected daily during the first week, and a single dose of 50 mg. three times a week during the next 8 weeks, with dramatic results, all the manifestations of nephrosis being diminished. By repeated electrophoresis the effect of ACTH on the serum protein levels was observed. The total protein content of the serum in the two cases increased from 3·1 and

4·5 g. per 100 ml. to 6·8 and 6·81 g. per 100 ml. respectively, mainly due to an increase in albumin content, the proportion of which rose from 5·7 and 10·9 per cent. to 49 and 35·5 per cent. respectively. The proportions of globulin, which was the most seriously affected fraction, soon rose to normal levels (from 2·5 and 1·3 per cent. to 3·8 and 3·9 per cent. of the total protein content respectively), whereas those of the α_2 and β fractions decreased. These observations confirm those reported by other authors. On the other hand the proportion of γ globulin changed in opposite directions in the two children—an unexplained observation. During the 5 months after withdrawal of ACTH the good results were maintained and no late untoward effect was noticed.

L. H. Worth.

Combined Corticotrophin Therapy and Chemotherapy in Pulmonary Tuberculosis. With Special Reference to Hypersensitive Reactions. HOUGHTON, L. E. (1954). *Lancet*, **1**, 595. 1 fig., 21 refs.

Although majority opinion is against using corticotrophin in the management of tuberculous patients, the author appears to have had considerable success with this method of treatment. At Harefield Hospital, Middlesex, a total of 21 patients aged from 5 to 60 years, all but five of whom had exhibited sensitivity to streptomycin or intolerance to PAS, or both, were given corticotrophin for about 7 weeks, beginning with 80 mg. daily and decreasing to 10 mg. daily. The latter, as a maintenance dose, was usually sufficient to control hypersensitivity. Although all the patients were suffering from extensive, active disease, none of them deteriorated radiologically and most of them improved markedly. In some cases corticotrophin appeared to act as an adjuvant to streptomycin, and there was no relapse when the hormone was withdrawn.

From a study of the case histories presented it is quite obvious that corticotrophin suppressed severe hypersensitivity reactions to streptomycin and PAS and that the hypersensitivity does not necessarily return on withdrawing the hormone, while it also appeared to control the gastro-intestinal symptoms brought on by PAS. Although corticotrophin has been shown to impede the action of streptomycin in experimental tuberculosis in guinea-pigs, the author does not regard this tendency as necessarily applicable to man. It is conceivable, he suggests, that the drug, by preventing early fibroblastic proliferation, brings a higher concentration of streptomycin to bear on the invading bacilli. It is obviously better, if possible, to kill off these bacilli at an early stage than for them to be locked-up with the fibroblasts and thus be potentially capable of causing a flare-up of the lesion in later years. As many of these patients, most of whom have been followed up for 2 years, were dejected and were deteriorating clinically before starting the corticotrophin treatment, the improvement, both physical and mental, seems to have been most gratifying.

[This is one of the most important of the recent contributions to the treatment of pulmonary tuberculosis and should be read by all phthisiologists.]

Paul B. Woolley.

Effect of Cortisone and Streptomycin on experimentally induced Pulmonary Tuberculosis in Rabbits. MORGAN, T. E., WANZER, S. H., and SMITH, D. T. (1954). *J. Bact.*, **67**, 257. 2 figs, 20 refs.

Effect of Corticotropin (ACTH) and Streptomycin on experimentally induced Pulmonary Tuberculosis in Rabbits. WANZER, S. H., MORGAN, T. E., and SMITH, D. T. (1954). *J. Bact.*, **67**, 264. 2 figs, 13 refs.

These two papers are concerned with experiments performed at Duke University School of Medicine, Durham, N. Carolina, which were designed to compare the effects of cortisone and corticotrophin (ACTH) on the progress of pulmonary tuberculosis in rabbits under treatment with streptomycin. All the animals employed in the experiments were of approximately the same weight, but of mixed sexes. [Presumably they were of the same strain; the authors describe them simply as white rabbits.] Some of the animals had previously been sensitized and partially immunized by the subcutaneous injection of a homogenate of living, avirulant tubercle bacilli. Infection was induced by the injection of a standard dose of *Mycobacterium tuberculosis* var. *bovis*, Ravenel strain, into the trachea, the rabbit being held so that the inoculum drained into the upper lobe of the right lung. The 149 rabbits so infected were divided into ten groups, four of which were unsensitized and six sensitized, and were treated as follows:

A. *Unsensitized Animals*:
   (I) controls (untreated);
   (II) streptomycin only;
   (III) cortisone or ACTH only (low dosage);
   (IV) streptomycin plus cortisone or ACTH (low dosage).

B. *Sensitized Animals*:
   (I) controls (untreated);
   (II) streptomycin only;
   (III) cortisone or ACTH only (low dosage);
   (IV) streptomycin plus cortisone or ACTH (low dosage);
   (V) cortisone or ACTH only (high dosage);
   (VI) streptomycin plus cortisone or ACTH (high dosage).

The rabbits died or were killed at different intervals and the extent of the disease determined.

In general the disease was much more extensive in the unsensitized than in the sensitized animals, while those receiving streptomycin were less severely affected than the rest. When cortisone was given alone in low dosage the lesions present in both sensitized and non-sensitized groups were more severe and more progressive than those seen in the controls, and when high doses were given the condition was fulminating and invariably fatal. Cortisone in low dosage plus streptomycin gave a picture similar to that seen with streptomycin alone, whereas the condition of the animals receiving cortisone in high dosage plus streptomycin was more like that of the untreated controls. In contrast to cortisone, ACTH in low dosage did not exert any damaging effect on the course of untreated tuberculosis, nor did it interfere with the beneficial effect of streptomycin. Even in high dosage it did not interfere with the action of strepto-

mycin, and when given alone the disease was only a little more severe than that seen in the controls. The low dosage of cortisone used (2 mg. daily) was approximately equivalent to the usual dosage for man (60 to 200 mg.), whereas the low dosage of ACTH (10 units daily) was well above the equivalent human dosage. The higher dosages of cortisone and ACTH were 20 mg. and 20 units daily respectively. Cortisone thus exerted a deleterious effect both at and above the normal dosage level, whereas no harmful effect was seen with ACTH until the dosage was twenty times greater than normal.

H. J. Bensted.

Influence of Cortisone on the Course of Clinical Ocular Tuberculosis. (Influenza del cortisone sul decorso delle tubercolosi oculari cliniche.) LEPRI, G. (1954). *G. ital. Oftal.*, **7**, 149. 24 refs.

The author reports the results given by a number of ophthalmologists on the effects of cortisone on the clinical course of ocular tuberculosis. It is favourable especially in "paratuberculous" diseases of the anterior part of the eye. In the granulomatous forms of tuberculosis there is a marked decrease in inflammation. In these cases the treatment must always be followed with special care and must be combined with antibiotics or chemotherapeutics. The retrobulbar route should be used in specific conditions only. Cortisone does not interfere with antibiotics and chemotherapeutics and in some cases enhances their activity. *N. Pagliarani.*

Cortisone and Ocular Tension. (Cortisone e tono oculare. (Ricerche cliniche con cortisone usato per istillazioni.)) COLOMBI, C. (1954). *Rass. ital. Ottal.*, **23**, 63. 5 refs.

In normal conditions, cortisone instilled into the conjunctival sac of young and old subjects had no influence on the ocular tension. *N. Pagliarani.*

Cortisone and the Eye. (Cortison und Auge.) STARK, H. (1954). *Klin. Mbl. Augenheilk.*, **124**, 584. 81 refs.

The author's experience with cortisone in ophthalmology is very much the same as that recorded in the Anglo-American literature. The references are mostly to well-known monographs and included French, Dutch, Italian, and other European sources. The statements made are impressions primarily, which could not be statistically evaluated, and the periods of observation are variable throughout. Long-term impressions are not discussed.

Corneal inflammations of non-bacterial and recent onset (cornea herpes), keratoplasty, iridocyclitis (postoperatively following cataract extraction), and vitreous haemorrhages constitute the main range for cortisone therapy. The claim that cortisone aids in the breakdown of synechiae would probably be contested.

L. Cudkowicz.

Investigations into the Mode of Action of Cortisone Therapy in Rheumatoid Arthritis. (Untersuchungen zur Wirkungsweise der Cortisonetherapie bei der primär chronischen Polyarthritis.) SCHMID, J., SCHIRMER, K., and WARUM, F. (1954). *Acta neuroveg.* (*Wien*), **8**, 489. 3 figs.

Should Cortisone and ACTH be used in Arthrosis? (L'emploi de la cortisone et de l'ACTH se justifie-t-il dans les arthroses?) FEROND, M. (1953). *Acta physiother. rheum. belg.*, **8**, 178.

Does Present Knowledge of the Pharmacodynamics of the Adrenal Corticoids Open the Field to a Wider Concept of Rheumatism? (Les données pharmacodynamiques actuelles sur les corticoïdes surrénaux ouvrent-elles le champ a une nouvelle conception plus éclectique du rhumatisme?) WAHL, M. (1954). *Rev. Rhum.*, **21**, 411. 43 refs.

Clinical and Experimental Problems relating to the Antiphlogistic Action of Hydrocortisone and Cortisone. (Problemi clinici e sperimentali relativi all'azione antiflogistica dell'idrocortisone e del cortisone.) ZACCO, M. (1954). *Reumatismo*, **6**, 207. 8 figs, 30 refs.

Other General Subjects

Rheumatic Manifestations provoked by Commissurotomy. (Les évolutions rhumatismales provoquées par la commissurotomie.) SOULIÉ, P., BOUVRAIN, Y., FORTIN, P., DI MATTEO, J., and TRICOT, R. (1954). *Arch. Mal. Coeur*, **47**, 49.

Among one hundred patients subjected to mitral commissurotomy, reactivation of acute rheumatism by the operation was thought likely or possible in ten cases, and in this paper these are discussed in some detail. It is pointed out that in order for a diagnosis of reactivation to be made, a sufficiently long interval of freedom from rheumatic symptoms before the operation must have elapsed, and that the diagnosis of acute rheumatic fever must be established with reasonable certainty, despite the absence of any specific diagnostic tests.

In four of the present cases it appeared that reactivation could reasonably be assumed as in three of them no evidence of any rheumatic activity had been present for 6, 13, and 30 years respectively, and in the fourth case the patient had never had acute rheumatic fever at any time. In these four cases the interval between operation and recrudescence ranged from 24 hours to 2 months. In another two cases the operation was performed too soon after a previous attack of rheumatic fever for the infection to be considered inactive at the time of operation, and in a further two the recurrence took place too long after the operation to be attributable to it. In the remaining two cases the rheumatic nature of the post-operative condition was doubtful. No relation was found between the degree of mitral stenosis, the condition of the valve, or the degree of surgical trauma and the likelihood of reactivation of acute rheumatism.

[Some relevant papers on the histological findings in biopsy specimens of the left auricle are discussed, but unfortunately without any bibliographical references; those interested in this aspect may wish to consult the following: Enticknap, *Brit. Heart J.*, 1953, **15**, 37; Decker and others, *Circulation*, 1953, **8**, 161.] *A. Schott.*

INDEX TO VOLUME XIII, 1954

* indicates that only the title of the article is given

Abu Mansur, 194
Achilles tendon, pathology of, in arthritis, rheumatoid, 43
Achillodynia, 50
Acid, hyaluronic, nature of, 361
——, hydrobenzoic in rheumatic fever, 60
——, salicylic, and oxygen consumption, 60
——, uric, aspirin and, 238
——, ——, in gout, 120, 233, 366
——, ——, probenecid and, 238
——, ——, in serum, phenylbutazone and, 318
——, ——, sodium salicylate and, 238
——, ——, urinary, 121
——, ——, ——, phenylbutazone and, 318
Acqui Prize, 1954, 257
Acromegaly, 53
Acroparaesthesia in spondylosis, 10
ACTH in ankylosing spondylitis, 109, 188
——, dosage schedule, 309
—— and pathological fractures, 363
——, production of, in conditions of stress, 102
—— and serum levels in rheumatic disease, 214
—— gel, highly purified, in rheumatoid arthritis, 56
ACTHAR: *See* ACTH
Acute rheumatism: *See* Rheumatism, acute
Adaptation syndrome, 102
Addison's disease, 9-α-fluoro hydrocortisone acetate in, 291
ADLER, E., and MAYBAUM, S.: Rare features in a case of Gaucher's disease, 229
Adrenal cortex and homeostasis, 346
Adrenalectomy, experimental, 103
Adrenocortical steroids, antiphlogistic influence of, 346
—— ——, metabolism of, in synovium, 347
Adrenogenital syndrome, 9-α-fluoro hydrocortisone acetate in, 291
Agglutination, sheep cell, 279, 302, 306
Albumin/globulin levels in plasma in arthritis and spondylitis, 209
Alexander of Tralles, 193
Allergens, streptococcal, hypersensitivity to, and arthritis, rheumatoid, 325
Allo-dihydro-hydrocortisone, 297, 354
*AMATULLI, G., 75
American Rheumatism Association Annual Meeting, 1954, Proceedings, 344
——, Cooperative Study of Cortisone Therapy in Rheumatoid Arthritis, Interim Report, 349
——, Presidential Address, 344
Amino acids and nutrition in rheumatism, acute, 324
Amyloidosis in arthritis, rheumatoid, 372 *bis*
Anaemia of arthritis, rheumatoid, 365
Androsterone, 67
Ankylosing spondylitis: *See* Spondylitis, ankylosing
Annulus, protrusion of, in intervertebral disk, 3
Appendicectomy, arthritis, rheumatoid, and, 341
Arab physicians, 194
Argyrophilia, 30
ARONOFF, A., *256, 373
Arteritis of arthritis, rheumatoid, 136
——, temporal, and rheumatic disease, 136
Artery, lesions of, and arthritis, rheumatoid, 277
Arthritis and Rheumatism Foundation, U.S.A., Cleveland Chapter, 257
Arthritis, classification of, 361
——, chronic, psycho-social factors in rehabilitation, 312
——, experimental, production of, 103
——, ——, response to cortisone, 105
——, ——, synovo-toxic antiserum tagged I^{311} in, 369
——, gouty, colchicine in, 367
——, ——, phenylbutazone in, 317
——, rheumatoid, anaemia of, 365
——, ——, amyloidosis in, 372 *bis*
——, ——, arteritis of, 136
——, ——, aspirin in, 351
——, ——, bone marrow in, 327
——, ——, and carcinoma, pulmonary, 52
——, ——, cortisone in, 201, 207, 302, 304, 349, 351, 352
——, ——, diphenylamine in, 372
——, ——, gold therapy, 201, 208
——, ——, —— —— and erythrocyte sedimentation rates, 336
——, ——, heel lesions in, 42
——, ——, histochemical study of nodules of, 28
——, ——, hormone therapy, analgesic and suppressive, in, 307
Arthritis, rheumatoid, hydrocortisone in, 297, 354 *bis*, 368, 373
——, ——, juvenile, spondylitis in, 364
——, ——, and keratoconjunctivitis sicca, 372
——, ——, metabolism of adrenal cortical steroids in synovia cavity, 347
——, ——, phenylbutazone in, 201, 208
——, ——, placental tissue implantation in, 63
——, ——, plasma proteins in, 201
——, ——, and polyarteritis nodosa, 277
——, ——, post-partum plasma in, 131
——, ——, procaine, intra-articular and, 373
——, ——, pulmonary changes in, 52, 373
——, ——, remissions in, 362
——, ——, shoulder lesions in, 157
——, ——, serum levels in, 212, 213
——, ——, surgery and, 341
——, ——, thyroidectomy in, 250
——, —— , zone electrophoresis in, 201
Arthropathy, pararheumatic and polyarteritis nodosa, 277
Arthroplasty in ankylosing spondylitis, 188
ASLING, C. W., 346
Aspirin and cortisone acetate in arthritis, rheumatoid, 351
Autopsy in polyarteritis, 277
Autumn crocus: *See* Colchicum

BACH, F. J., *74, *75
*BADIN, J., 167
BAIRD, J. P., 74
*BALL, J., 373
——: Rheumatoid arthritis and polyarteritis nodosa, 277
BARKIN, R., 364
BARTFELD, H., 70
Batchelor's pseudarthrosis, 188
*BATTEN, G., 75
BAUER, W., 352, 362
Bauhin, Caspar, 194
BAYLES, T. B., 348, 365, 369
BEATTIE, J. W., 256
BEAUREGARD, J. M., 362
"Benemid": *See* Probenecid
BERGENSTAL, D. M., 360
Bicillin: *See* N,N' Dibenzylethylenediamine dipenicillin G
BICKELL, W. H., 353
Bile-duct, obstruction of, and suppression of inflammation, 102
BILLIMORIA, J. D., 164
Biopsy of heel in rheumatoid arthritis, 47
—— in polyarteritis, 277
—— of sternal bone marrow, 327
—— of synovium in diagnosis, 353
BLÉCOURT, J. J. DE: "Screening" of the population for rheumatic diseases, 338
Blood, complementary activity of, in rheumatic disease, 211
——, electrophoresis in study of, 201
——, pregnancy, in rheumatoid arthritis, 133
—— vessels, peripheral, cortisone and, 302
BLUMBERG, B., 361
Bock, Hieronymus, 195
BOLAND, E. W., 348
——, and HEADLEY, N. E.: Preliminary clinical trials with 9-alpha-fluoro hydrocortisone acetate in rheumatoid arthritis, 291
Bone, histology and radiology of, in spondylitis, 222
—— marrow in arthritis, rheumatoid, 327
BOOK REVIEWS:
ASBOE-HANSEN, G. (edited by): Connective tissue in health and disease, 1954, 371
BUETTI-BAUML, C.: Funktionelle röntgendiagnostik der halsweibsaüle, 1954, 372
BYWATERS, E. G. L.: Canadian Red Cross Memorial Hospital Report, 1953, 252
COPEMAN, W. S. C.: West London Hospital Report, 1953, 252
CYRIAX, J.: Textbook of orthopaedic medicine. Vol. I. Diagnosis of soft tissue lesions, 1954, 370
FLETCHER, E. T. D.: Royal Free Hospital Report, 1953, 252
HOULI, J.: Espondilite anquilosante, 1954, 370
REVISTA ESPAÑOLA DE REUMATISMO: VIII Congreso Internacional de Enfermedades Reumaticás, 1953, 163
ROTÉS-QUEROL, J.: Tratamiento de los Reumatismos, 252
STEINBERG, C. L.: Arthritis and rheumatism: the diseases and their treatment, 1954, 370

BOOK REVIEWS:
TRAUT, E. F.: Rheumatic Diseases, 1952, 71
WHO Expert Committee on Rheumatic Diseases. First Report, 1954, 253
*BOSCH, S. J., 167
BOWIE, M. A., 354
——: *See* HOLLANDER, J. L., BROWN, E. M., Jr., JESSAR, R. A., UDELL, L., SMUKLER, N., and BOWIE, M. A.
BRAIN, R.: Heberden Oration, 1953. Spondylosis: The known and the unknown, 2
*——, 72
Brazil, chair of rheumatology, 71, 167
BRENNER, J. M., 256
British Empire Postgraduate Medical Federation, 375
British Rheumatic Association, 71
BRODIE, B. B., 347
BROOMHEAD, R., 256, *374
BROWN, E. M., 354
BROWN, E. M., Jr.: *See* HOLLANDER, J. L., BROWN, E. M., Jr., JESSAR, R. A., UDELL, L., SMUKLER, N., and BOWIE, M. A.
*BROWN, P., 167
Brunschwig, Hieronymus, 194
*BULASHENKO, H., 75
BUNIM, J. J., 347, 348, 352, 365
Bursitis, sub-Achilles, 50
——, sub-acromial, 159
Butazolidin: *See* Phenylbutazone
BYWATERS, E. G. L.: Heel lesions of rheumatoid arthritis, 42
——, *256, 373 *bis*
Byzantine physicians, 194

*CAHN, J., 75
Calcification, para-articular, in paraplegia, 372
Calcinosis of vessels and joints, heredo-familial, 15
CALKINS, E., 352
Canadian Rheumatism Association, Officers, 1954-55, 257
Carcinoma of lung simulating rheumatoid arthritis, 52
Carditis, rheumatic, and arthritis, rheumatoid, 137
——, ——, in children, 359
Caronamide and uric acid excretion, 234
Cartilage, biopsy of, 224
—— degeneration in arthritis, rheumatoid, 42
—— extracts and inhibition of cortisone effect, 361
——, pannus in, 285, 286, 287
——, radioactive sulphur uptake of, hypophysectomy and, 360
*CASOLO, G., 75
CATCHPOLE, B. N., JEPSON, R. P., and KELLGREN, J. H.: Peripheral vascular effect of cortisone in rheumatoid arthritis, scleroderma, and other related conditions, 302
*CAYLA, F., 257
CECIL, R. L., 350, 362
Cervical spine, pathology of, 9, 11
Chartered Society of Physiotherapists, Annual Congress, 1954, 374
CHATELIN, N. H., 368
Children, haemolytic streptococcal infection in, 355
——, rheumatic carditis in, 359
——, spondylitis and arthritis in, 364
Cholecystectomy, arthritis, rheumatoid, and, 341
Circulation of blood, cortisone and, 302
CLARK, W. S., 363
Cleveland, Ohio, 257
Colchicine in gout, 163, 190, 233
——, intravenous, in gouty arthritis, 367
——, isolation, chemistry, and action of, 196
——, radioactive, C_{14} labelled, 197
—— in tumours, 197
Colchicum, history of use in gout, 190
Collagen disease, hormone therapy in, 310
—— ——, rheumatism, acute, as, 324
——, presence of, in nodules, 30
Collagenase, action of, on nodules, 28
*COLLICELLI, A., 75
CONGRESSES:
American Rheumatism Association, 344
Arthritis and Rheumatism Foundation, 257
British Rheumatic Association, 71
Chartered Society of Physiotherapists, 375
European League against Rheumatism, 373
Heberden Society, 72, 74, 255, 256, 372, 373
New York Rheumatism Association, 167
CORRESPONDENCE:
Colchicine in gout, 163
Trafuril, 70
Corticoids, antiphlogistic effect of, 102
Corticosteroids, 56
Corticotrophin: *See* ACTH
Cortisone in arthritis, rheumatoid, 201, 252 *bis*, 349, 351
—— acetate and aspirin in arthritis, rheumatoid, 351
——, dosage schedule, 309
—— and erythrocyte sedimentation rate, 302
—— and experimental inflammation, 103
—— inhibition by cartilage extracts, 361
Cortisone metabolism in long-term therapy, 352
—— and pathological fractures, 363
—— and peripheral vessels, 302
—— and plasma, rate of disappearance from, 347
—— in Reiter's syndrome, 161
—— and serum levels in rheumatic disease, 214
—— and skin temperature, 304
—— in spondylitis, ankylosing, 188, 201
COURSES:
British Empire Postgraduate Medical Federation, 1955, 375
Empire Rheumatism Council, 1955, 375
Fellowship of Postgraduate Medicine, 1854, 75
Rome Rheumatology Day, 1954, 75
University of Havana, 1954, 257
Coxsackie virus infection, histopathology of sarcolemma and sarcoplasm in, 35
Cramp, 331
Creatinine excretion, 317
*CRITTENDEN, J. O., 75
Crocus, autumn: *See* Colchicum
CRUICKSHANK, B.: The arteritis of rheumatoid arthritis, 136
COBB, S., 361
*COLLINS, D. H., 373
*CUDKOWICZ, L., 75
Culpeper, Nicolas, 195
*CURTARELLI, G., 75
CURTISS, P. H., 363

*DALEY, R., 75
*DARBY, P. W., 74
DE COEK, N., 372
*DELBARRE, F., 257
Demetrius Pepagomenus, 194
DENKO, C. W., 360
Dermatitis in gold therapy, 337
Dermatomyositis and arteritis, 136
——, cortisone and, 303
——, hormone therapy in, 310
Desoxycorticosterone acetate (DOCA) and experimental inflammation, 103
Diabetes and rheumatism, acute, 325
Diet and rheumatism, acute, 324
Dinitro-o-cresol, 61
Dioscorides, 192
Diphenylamine reaction in arthritis, rheumatoid, 372
Disk, intervertebral, biopsy of, 224
——, ——, degeneration of, 2
DIXON, A. ST. J., 366
DOCKERTY, M. B., 353
DODGE, H. J., 359
*DOHAN, F. C., 75
DOUGHERTY, T. F., 346
*DRESNER, E., 373
Dropsy, colchicum in, 195
DUCKETT JONES, T., 358
DUFF, I. F., 354, 369

Editorial, 1, 101, 185
Eggs and protein deficiency in rheumatism, acute, 324
*EHRLICH, M. E., 167
Electromyograph studies of painful muscles, 331
Electrophoresis in study of plasma proteins, 201
*ELLIS, M., 374
*ELLMAN, P., 75
EMERSON, C. P., 365
Empire Rheumatism Council:
17th annual report, 164
Officers, 1954-55, 166
Course for consultants, 1955, 375
Endocarditis, bacterial, and arteritis, 136
Endotoxins and fibrinoid necrosis, 359
ENGFELDT, B., ROMANUS, R., and YDÉN, S.: Histological studies of pelvo-spondylitis ossificans (ankylosing spondylitis) correlated with clinical and radiological findings, 219
Enzyme preparations, action of, on nodules, 28
Eosinophil reactions and gold therapy, 337
Eosinophilia in arthritis, rheumatoid, 328
Ephemeron: *See* Colchicum
Erosion in heel bones, 51
Erythema, palmar, 53
Erythrocyte sedimentation rate, cortisone and, 302
—— —— ——, gold therapy and, 336
—— —— ——, plasma fibrinogen level and, in arthritis and spondylitis, 201
Etiocholanolone, 67
Euricius Cordus, 194
European League against Rheumatism, 373
EVANS, H. M., 346

FAIRBANKS, R., *167, 347
FAVOUR, C. B., 369

FAWNS, H. T., and LANDELLS, J. W.: Histochemical studies of rheumatic conditions. II. The nodule of rheumatoid arthritis, 28
FEARNLEY, G. R., *256 *ter*, 372 *bis*, 373 *bis*
Fellowship of Postgraduate Medicine, Rheumatism course, 1954, 75
Fever, rheumatic: *See* Rheumatism, acute
Fibrinogen level in plasma, 201
Fibrinoid, presence of, in nodules, 31
Fibrosis of nerve roots, 7
Fibrositis, 331
FINCH, S. C., 365
FINN, N., 163
FLETCHER, ERNEST, 362
*FLETCHER, E. T. D., 167
FORESTIER, J., 74
*FOSTER, V., 167
Fractures, pathological, and steroid hormone therapy, 363
Franklin, Benjamin, 195
*FREEDMAN, A., 74
FREIREICH, E. J., 365
FREYBERG, R. H., 354, 365
"Frozen" shoulder, 159
—— ——, novocaine in, 231
Fuchs, Leonhart, 194

GEIGER, J.: *See* NEUSTADT, D. H., GEIGER, J., and STEINBROCKER, O.
Galen, 193
Garrod, work on gout, 196
Gastro-intestinal symptoms in hormone therapy, 308
Gaucher's disease, 229
Geoffroy, Stephen Francis, 195
*GEORGES, G., 75
GIBSON, G., and NORYMBERSKI, J. K.: A note on the rapid assay of 17-ketogenic steroids in urine, 59
Gilbertus Anglicus, 194
Girdlestone's pseudarthrosis, 188
Glucocorticoid properties of hydrocortisone, 291
Glutathione metabolism, 325
Gold therapy in arthritis, rheumatoid, 201
—— —— in spondylitis, ankylosing, 201
—— —— complications and erythrocyte sedimentation rate, 336
GOLDTHWAIT, J. C., 369
GOODSON, W. H., Jr., 356
*GOULD, I., 167
Gout and arteritis, 136
——, colchicum in, 163, 190, 367
——, probenecid in, 120, 233
——, sodium salicylate in, 233
——, uric acid excretion in, 366
GRAHAM, W., 367
Granuloma annulare and arteritis, 136
Greek physicians, 193
Greven, Jaques, 195
Group-A haemolytic streptococci in rheumatism, acute, 324
Growth hormone and arthritis, experimental, 346
—— —— and radioactive sulphur uptake of cartilage, 360
GUERRA, S. L., 347
GUTMAN, A. B., *167, *257, 366

HALL, D. A., 255
Halogen derivatives of hydrocortisone, 291
*HARDING, H. E., 75
*HARRISON, M. H. M., 373
HART, F. DUDLEY, 74, *75, 164
——: Ankylosing spondylitis: a survey, 186
HARTFALL, S. J., *75, 256, *374
HARTUNG, E. F., 70
——: History of the use of colchicum and related medicaments in gout, 190
Havana, University of, Summer School, 1954, 257
*HAYDU, G. G., 167
HEADLEY, N. E.: *See* BOLAND, E. W., and HEADLEY, N. E.
HEALD, L.: *See* LOWMAN, E. W., MILLER, S., LEE, P. R., STEIN, H., KING, R., and HEALD, L.
Heberden Oration, 1953, 2
—— ——, 1954, 256, 372
—— Round, 1954, 255
—— Society Annual Dinner, 1953, 72
—— —— —— ——, 1954, 256
—— —— Annual Meeting, 1954, 256
—— —— Annual Report, 1953, 72
—— —— Clinical Meetings: December 5, 1953, 74
February 26, 1954, 74
May 8, 1954, 256
September 25, 1954, 256
December 4, 1954, 375
Heel lesions in rheumatoid arthritis, 42
HENCH, P. S., 352, 353
Henoch-Schönlein purpura and arteritis, 136
Herbstzeitlose: *See* Colchicum
Heredity and calcinosis, 15
—— and spondylitis, ankylosing, 186
HERNDON, C. H., 363
Hermodactyl: *See* Colchicum
Herniation of intervertebral disks, 2
HILL, R.: *See* HUFFMAN, E. R., WILSON, G. M., SMYTH, C. J., and HILL, R.
Hip joint, injection into, 246
HIRSCHFELD, I., 358
Histology of bone marrow in arthritis, rheumatoid, 328
—— of polyarteritis nodosa, 277
—— of spondylitis, ankylosing, 220
HOLLANDER, J. L., *75, 347, 354, 368
——, BROWN, E. M., JR., JESSAR, R. A., UDELL, L., SMUKLER, N., and BOWIE, M. A.: Local anti-rheumatic effectiveness of higher esters and analogues of hydrocortisone, 297
HOLOPAINEN, T. E.: *See* LAINE, V. A. I., VAINIO, K. J., and HOLOPAINEN, T. E.
Homeostasis, adrenal cortex in, 346
Hormone therapy, analgesic, 307, 354
—— —— by placental tissue implantation, 65
—— ——, suppressive, 307, 354
HOULI, J., 71, 167
——, and MONTEIRO MARINHO, H.: Bone marrow in rheumatoid arthritis, 327
H.P. Acthar Gel: *See* ACTH
HUFFMAN, E. R., WILSON, G. M., SMYTH, C. J., and HILL, R.: Metabolic effect of phenylbutazone in gouty and non-gouty arthritis, 317
——, 366
HUMBLE, J. G., 74
HUNT, T. E., and TREW, J. A.: Zone electrophoretic studies of plasma proteins in rheumatoid arthritis and ankylosing spondylitis, 201
Husson, Nicolas, 196
Hyalase, action of, on nodules, 28
Hydrobenzoic acid and oxygen consumption, 60
Hydrocortisone, 109
—— acetate, intra-articular, 297
—— ——, 9-alpha-fluoro, in arthritis, rheumatoid, 291
—— benzoate, 297, 354
—— caprylate, 297, 354
—— free alcohol, 293
——, higher esters and analogues of, intra-articular, 297, 354
—— intra-articular, 246, 368, 373
—— and plasma, rate of disappearance from, 347
—— t-butyl acetate, 297, 354
Hyperaemia time, cortisone and, 305
Hyperglobulinaemia, 325
Hypophysectomy and radioactive sulphur uptake of cartilage, 360

I^{131} and experimental arthritis, 369
Ibn-El-Beithar, 194
Implantation of placental tissue in rheumatoid arthritis, 63
Incidence of rheumatic disease, 253, 338
Inflammation, suppression of, by systemic stress, 102
INGLE, D. J., 346
Injection of hip joint, 246
Insulin and rheumatism, acute, 325
Intestine, polyarteritis nodosa in small artery of, 285
Iritis and spondylitis, ankylosing, 187
*IRVINE, J. H., 167
Italian Society of Rheumatology, 75, 257

JÄRVINEN, K. A. J., and KUMLIN, T.: Carcinoma of the lung simulating early rheumatoid arthritis, 52
Jaundice, obstructive, and inflammation, 102
JEPSON, R. P.: *See* CATCHPOLE, B. N., JEPSON, R. P., and KELLGREN, J. H.
JESSAR, R. A., 354
——: *See* HOLLANDER, J. L., BROWN, E. M., JR., JESSAR, R. A., UDELL, L., SMUKLER, N., and BOWIE, M. A.
Joint, acromio-clavicular, 158
——, biopsy of, 222
——, calcinosis of, familial, 15
——, erosion of, 283, 287
——, fibrosis in, 283, 287
—— involvement in spondylitis, ankylosing, 187
——, sacro-iliac, in osteitis condensans ilii, 150
——, scapulo-humeral, 157
——, sterno-clavicular, 158
—— tissue, polyarteritis nodosa in, 281
Jones, Edwin Godden, 196
*JONES, T. DUCKETT, 257

KALLIOMÄKI, L.: Correlation of the erythrocyte sedimentation rate and gold complications in rheumatoid arthritis, 336
——: Role of various surgical operations in the history of patients with rheumatoid arthritis, 341
KAMMERER, W. H., 367
KCl, 309
*KEECH, M., 373
KELLETT, C. E.: Complementary activity of the blood in rheumatism and certain allied disorders, 211

KELLEY, V. C., 356
KELLGREN, J. H., 373
——: *See* CATCHPOLE, B. N., JEPSON, R. P., and KELLGREN, J. H.
*KENDELL, H. W., 257
KENYON, A. T., 360
Keratoconjunctivitis sicca and arthritis, rheumatoid, 372
*KERSLEY, G. D., 373
KEY, J. A., 369
Kidney function in gout, 366
——, perivascular fibrosis, 284
——, polyarteritis nodosa in, 287
KING, R.: *See* LOWMAN, E. W., MILLER, S., LEE, P. R., STEIN, H., KING, R., and HEALD, L.
KINSELL, L. W.: Suppressive as compared with analgesic hormonal therapy in patients with rheumatoid arthritis, 307
——, 354
*KLEIN, R., 167
Klippel-Feil deformity of shoulder, 159
Knee, hydrocortisone injections into, 297
KOMINZ, J. S., 368
KOUMANS, A. K. J.: *See* LANDSMEER, J. M. F., and KOUMANS, A. K. J.
KUMLIN, T.: *See* JÄRVINEN, K. A. J., and KUMLIN, T.

LACKNER, R., *256 *ter*, 372 *bis*, 373
*LAI, L., 75
LAINE, V. A. I., VAINIO, K. J., and PEKANMÄKI, K.: Shoulder affections in rheumatoid arthritis, 157
——, ——, and HOLOPAINEN, T. E.: Effect of thyroidectomy in rheumatoid arthritis, 250
LANDELLS, J. W.: *See* FAWNS, H. T., and LANDELLS, J. W.
LANDSMEER, J. M. F., and KOUMANS, A. K. J.: Anatomical considerations in injection of the hip joint, 246
LATTES, R., 361
"L.E." cells in arthritis, rheumatoid, 328
LEE, P. R.: *See* LOWMAN, E. W., MILLER, S., LEE, P. R., STEIN, H., KING, R., and HEALD, L.
LEONARD, J. C., 74, *373
Leukopenia and gold therapy, 337
LI, C. H., 346
LICHTY, J. A., 359
Liga Mexicana contra el Reumatismo: *See* Mexican League against Rheumatism
Ligue Européenne contre le Rhumatisme: *See* European League against Rheumatism
Linnaeus, Carl, 195
Liver, role of, in suppressing inflammation, 102
——, polyarteritis nodosa in, 282, 284
*LLOYD ROBERTS, G. C., 373
*LOEWI, G., 373
LONG, D. A.: Rheumatic fever as a collagen disease, 324
*LOWMAN, E. W., 167
——, MILLER, S., LEE, P. R., STEIN, H., KING, R., and HEALD, L.: Psycho-social factors in rehabilitation of the chronic rheumatoid arthritic, 312
*LUCHERINI, T., 75
Lumbar spine, pathology of, 12
*LUNEDI, A., 75
Lung, carcinoma of, simulating early rheumatoid arthritis, 52
—— changes in arthritis, rheumatoid, 373
Lupus erythematosus and arteritis, 136
—— ——, fibrinoid deposits in, 359
—— ——, hormone therapy in, 310
—— ——, serum levels in, 212, 215

MACDONALD, C., 365
MCEWEN, C., *167 *bis*, 347, 349, 352
MACLAGAN, N. F., 164
MACLEOD, I., 166
*MACE, B. E. W., 373
*MAGGI, C. A., 75
*MANCINI, B., 75
Manipulation, contraindicated in ankylosing spondylitis, 188
Marie-Strümpell's disease: *See* Spondylitis, ankylosing
Marrow, bone, in arthritis, rheumatoid, 327
MARSON, F. G. W.: Sodium salicylate and probenecid in the treatment of chronic gout, 233
*——, 256
*MARTIN, E., 75
MARTIN, J. R., 361
MASON, R. N.: Studies on the effect of probenecid ('Benemid') in gout, 120
*MASTURZO, A., 75
MATTHEWS, B. F., 164
Mattioli, 195
MAYBAUM, S.: *See* ADLER, E., and MAYBAUM, S.
MEADE, B. W.: Effect of certain hydroxybenzoic acids on the oxygen consumption of Wistar rats, 60
*MEANOCK, I., 256
MEANOCK, R. I., 373
*MELLONI, F., 75
MERCHANT, W., 361
Mesue, John, 194
Metabolism of adrenal cortical steroids in synovial cavity, 347
——, phenylbutazone and, 317
Mexican League against Rheumatism, 375
MEYER, K., 361
MIKKELSEN, W. M., 368
MILLER, S.: *See* LOWMAN, E. W., MILLER, S., LEE, P. R., STEIN, H., KING, R., and HEALD, L.
Mineralocorticoid properties of hydrocortisone, 291
MISSEN, G. A. K., 372
MITCHELL, D. M., 352
MONTEIRO MARINHO, H.: *See* HOULI, J., and MONTEIRO MARINHO, H.
MOON, H. D., 346
Morphology of spondylitis, ankylosing, 227
MORRISON, R. J. G., 74
*MOTTA, L., 75
MUIR, I. H. M., 165
Muscle activity, electrical recording of, 332
—— fibre, diameter of, in Coxsackie virus infection, 35
—— spasm as cause of pain, 331
—— tissue, polyarteritis nodosa in, 282
——, wasting of, in cervical spondylosis, 10
Myelopathy in spondylosis, 11

N,N' Dibenzylethylenediamine dipenicillin G, in rheumatism, acute, 358
Necrosis, fibrinoid, endotoxins and, 359
Nephritis, serum levels in, 212
Nerve, radicular, fibrosis of, 7
Nervous system, disk degeneration and, 2
Netherlands, incidence of rheumatism in, 338
——, III European Congress of Ligue Européenne, 1955, 373
Neuritis, foraminal pressure and lumbar disk protrusion, 12
Neurology of osteo-arthritis of cervical spine, 363
NEUSTADT, D. H., GEIGER, J., and STEINBROCKER, O.: Effect of postpartum plasma in rheumatoid arthritis, 131
NEUWIRTH, E., *167, 363
New York Rheumatism Association, Annual Meeting, 1954, 167
NEWNS, G. R.: *See* WEST, H. F., and NEWNS, G. R.
Nicander, 192
*NICOLA, P. DE, 75
Nodes, articular, 18
Nodules, 350
——, histochemical studies of, 28
——, subcutaneous, 279
Nomenclature of rheumatic disease, 253
NORYMBERSKI, J. K., 164
——: *See* GIBSON, G., and NORYMBERSKI, J. K.
Novocaine in "frozen shoulder", 231
Nucleus, herniation of, in intervertebral disk, 3
Nuffield Foundation, grants for research, 374
Nutrition and rheumatism, acute, 324

Oedema of heel in rheumatoid arthritis, 50
Oophorectomy, arthritis, rheumatoid, and, 341
*ORTONA, L., 75
Osteitis condensans ilii and ankylosing spondylitis, 147
Osteo-arthritis and arteritis, 136
—— of cervical spine, neurology of, 363
—— and Gaucher's disease, 230
——, hydrocortisone analogues in, 297
—— of shoulder, 159
——, Trafuril in, 70
Osteo-arthropathy, experimental, induced by growth hormone, 346
——, pulmonary, due to carcinoma of lung, 54
Osteophytes in spondylosis, 7
OSTER, G., 361
Oxygen, consumption of, and hydrobenzoic acid, 60

Pain, muscular, electromyographic studies of, 331
—— in spondylosis, 10
Pancreas, polyarteritis nodosa in, 280
Paraplegia, para-articular calcification in, 372
Paré, Ambroise, 195
Paul of Aegina, 194
PEKANMÄKI, K.: *See* LAINE, V. A. I., VAINIO, K. J., and PEKANMÄKI, K.
Pelvis, calcinosis of, 20
Pelvo-spondylitis ossificans: *See* Spondylitis, ankylosing
Pemphigus, hormone therapy in, 310
Pepsin, action of, on nodules, 33
Periarthritis of shoulder, 159
Periodic acid—Schiff (P.A.S.), 28
Personality of rheumatoid patients, 312
PETERSON, R. E., 347
*PETTY, H., 374
Pharmacopoeia, colchicum derivatives in, 195
Phenylbutazone in arthritis, rheumatoid, 201
—— ——, gouty, 317
—— in spondylitis, ankylosing, 188, 201
—— and uric acid excretion, 318
——, uricosuric effect of, 321

Phosphotungstic acid—haemotoxylin (P.T.A.H.), 28
Physiotherapy in ankylosing spondylitis, 188
*PIACENTINI, G., 75
*PIERRE, R., 75
PIRKIS, J., 372
Pituitary-adrenal system in rheumatism, acute, 356
Placenta, implantation of, in rheumatoid arthritis, 63
Plasma, cortisone and hydrocortisone metabolism in, 347
——, post-partum, in rheumatoid arthritis, 131
—— proteins, electrophoresis in study of, 201
——, uric acid in, in gout, 124
Plasmocytosis in bone marrow in arthritis, rheumatoid, 328
*PLISHUK, F., 167
PLOTZ, C. M., *167 *bis*, 350
POLLEY, H. F., 353, 367
Polyarteritis nodosa and arthritis, rheumatoid, 136, 277
Polyarthritis and arterial lesions, 278
Polyvasculitis, hormone therapy in, 310
POND, M. H.: 17-ketosteroid excretion in two unusual forms of rheumatoid disease, 67
*PORRO, F., 75
PORTER, J. L., 164
POTTER, T. A., 364
Pregnancy and arthritis rheumatoid, 133
Preputial glands, response to cortisone, 105
*PREZIOSI, P., 75
Probenecid in gout, 120, 233
Procaine, intra-articular, in arthritis, rheumatoid, 373
—— and uric acid excretion, 234
Protein deficiency and rheumatism, acute, 324
——, plasma, electrophoresis of, 201
Proteinuria and erythrocyte sedimentation rate, 337
Pseudarthrosis in ankylosing spondylitis, 188
Psychosis in hormone therapy, 308
Psycho-social factors in rehabilitation of chronic arthritic, 312
*PUDDU, V., 75
*PURKISS, J., 256
*PURSER, J. A., 75

Quincy, John, 195

Radiology of Gaucher's disease, 230
—— of heel in arthritis rheumatoid, 44
—— of spondylitis, ankylosing, 188, 219
Radiotherapy in ankylosing spondylitis, 188, 201
RAGAN, C., 344, 361
*RAMMELKAMP, C. H., 257
RANTZ, L. A., 355
*RAWLS, W. B., 167
Reflex dystrophy, sympathetic, 159
Rehabilitation of arthritic, psycho-social factors in, 312
REID, H. A.: Reiter's syndrome and cortisone, 161
REIDY, J. P., 74
Reiter's syndrome, cortisone in, 161
Remissions in arthritis, rheumatoid, 362
RESEARCH:
  Empire Rheumatism Council, 164
  Hospital Reports, 252
  Italy: Acqui Prize, 257
  Nuffield Foundation Grants, 374
  Professorship of Rheumatology, Brazil, 71, 167
  World Health Organization, 253
REYNOLDS, W. E., 362
Rheumatic fever: *See* Rheumatism, acute
Rheumatism, acute, amino acids in, 324
——, ——, and arteritis, 136
——, ——, Bicillin prophylaxis in, 358
——, ——, as collagen disease, 324
——, ——, cortisone in, 325
——, ——, diabetes and, 324
——, ——, diet and, 324
——, ——, with Gaucher's disease, 229
——, ——, hormone therapy in, 310
——, ——, hydrobenzoic acid in, 60
——, ——, insulin in, 325
——, ——, pituitary-adrenal system in, 356
——, ——, salicylic acid in, 60
——, ——, serum levels in, 212, 213
Rheumatoid arthritis: *See* Arthritis, rheumatoid
*RICHARDSON, E. M., 75
ROBERTS, J. B., 367
ROBINSON, W. D., *257, 368
Roman physicians, 193
ROMANUS, R.: *See* ENGFELDT, B., ROMANUS, R., and YDÉN, S.
ROSENBERG, E. F., 364
ROSS, J. F., 365
*RUDD, E., 167
RUSOFF, J. H., 358
Ryff, Walther Hermann, 195

SAMMAN, P. D., 74
Sarcolemma, histopathology of, in Coxsackie virus infection, 35
Sarcoplasm, histopathology of, in Coxsackie virus infection, 35
*SARGENT, F., 75
Scapulo-costal syndrome, 160
*SCHWARTZ, L. L., 167
*SCHUBERT, M., 373
Sciatica, 12
Scleroderma and arteritis, 136
——, cortisone and peripheral vessels in, 302
——, hormone therapy in, 310
Sclerosis, systemic, cortisone and, 303, 304
Scribonius Largus, 193
*SCURO, L. A., 75
SELYE, H.: On the mechanism through which obstructive jaundice influences inflammatory processes, 102
Serapion Junior, 194
Serum levels in rheumatism, acute, 211
—— urate levels and phenylbutazone, 317
—— uric acid levels in gout, 123, 236
*SÈZE, S. DE, 257
*SFOGLIANO, C., 75
SHARP, J.: Heredo-familial vascular and articular calcification, 15
SHORT, C. L., *257, 362
Shoulder, "frozen", and cervical spondylosis, 10
—— lesions in rheumatoid arthritis, 157
Side-effects, 350
*SIGNY, G., 75
SIMPSON, M. E., 346
SIROTA, J. H., 366
Sjögren's syndrome, 17-ketosteroid excretion in, 67
Skin temperature, cortisone and, 303
SMITH, R. T., 368
Smith-Petersen's cup arthroplasty, 188
SMYTH, C. J., 367
——: *See* HUFFMAN, E. R., WILSON, G. M., SMYTH, C. J., and HILL, R.
SMUKLER, N., 354
——: *See* HOLLANDER, J. L., BROWN, E. M., JR., JESSAR, R. A., UDELL, L., SMUKLER, N., and BOWIE, M. A.
Società Italiana di Reumatologia: *See* Italian Society of Rheumatology
SOCIETIES:
  American Rheumatism Association, 344
  Arthritis and Rheumatism Foundation, 257
  British Empire Postgraduate Medical Federation, 375
  British Rheumatic Association, 71
  Canadian Rheumatism Association, 257
  Chartered Society of Physiotherapy, 374
  Empire Rheumatism Council, 164, 166, 375
  European League against Rheumatism, 373
  Fellowship of Postgraduate Medicine, 75
  Heberden Society, 72, 74, 255, 256, 372, 373
  Italian Society of Rheumatology, 75, 257
  Mexican League against Rheumatism, 375
  New York Rheumatism Association, 167
Sodium salicylate in gout, 233
*SOLOMON, W., 257
Somatic pain and muscle spasm, 331
Spine, biopsies of, 221
——, calcinosis of, 21
——, cervical, osteo-arthritis of, 363
——, deformity of, in osteitis condensans ilii, 151
——, pathology of, 7
Spleen, response to cortisone, 105
Splenectomy and Gaucher's disease, 229
Spondylitis, ankylosing, and ACTH, 109
——, ——, and arteritis, 136
——, ——, cortisone in, 207
——, ——, gold in, 208
——, ——, histological studies of, 219
——, ——, 17-ketosteroid excretion in, 67
——, ——, and osteitis condensans ilii, 147
——, ——, phenylbutazone in, 208
——, ——, plasma proteins in, 201
——, ——, radiotherapy in, 201
——, ——, serum levels in, 212, 216
——, ——, survey of, 186
—— in arthritis, rheumatoid, juvenile, 364
Spondylosis, survey of, 2
Staining of sections of nodules, 28
STECHER, R. M., 256, *372
STEIN, H.: *See* LOWMAN, E. W., MILLER, S., LEE, P. R., STEIN, H., KING, R., and HEALD, L.
STEINBERG, C. L., 360
*STEINBROCKER, O., 167
——: *See* NEUSTADT, D. H. GEIGER J., and STEINBROCKER, O.
STILLMAN, J. S., 364
Stoerck, Anton, 195
STOLLERMAN, G. H., 358
STOREY, G. O., *256, 372
STRANDBERG, B.: Histopathological changes in sarcolemma and sarcoplasm in Coxsackie virus infection, 35

Streptococcus, Group -A, prophylaxis in rheumatism, acute, by Bicillin, 358
—— haemolyticus infections in childhood, 355
Stress, antiphlogistic effect of, 102
Strumectomy: *See* Thyroidectomy
Subluxation of joints, 19
Sulphur metabolism and arthritis, rheumatoid, 325
——, radioactive, uptake of, and hypophysectomy, 360
Surgery and arthritis, rheumatoid, 341
Surugen: *See* Colchicum
Sydenham, Thomas, 195
Synovial fluid, physico-chemical investigation of, 362
Synovium, hydrocortisone in, 297
——, metabolism of adrenal cortical steroids in, 347
——, punch biopsy of, in diagnosis, 353

TAVERNER, D., 255
——: Muscle spasm as a cause of somatic pain, 331
TAYLOR, J. E. DUNCAN, 372
Tendinitis, 158
Tenosynovitis, 158
Theophrastus of Eresus, 192
THOMAS, L., 359
*THOMPSON, M., *74, *256, 372
——: Osteitis condensans ilii and its differentiation from ankylosing spondylitis, 147
Thoracic spine, pathology of, 12
Thymus response to cortisone, 104
Thyroidectomy in arthritis, rheumatoid, 250, 341
*TILLIS, H. H., 167
Tonsillectomy and arthritis, rheumatoid, 341
Tophi in gout, 233
*TOSTI, E., 75
Toxicity in hormone therapy, 308
—— in hydrocortisone therapy, 295
Toxicology of colchicine, 197
Trafuril, 70
Trauma, surgical, arthritis, rheumatoid, and, 341
TREW, J. A.: *See* HUNT, T. E., and TREW, J. A.
Trypsin, action of, on nodules, 33
TWEED, J. M., 164

UDELL, L., 354
——: *See* HOLLANDER, J. L., BROWN, E. M., JR., JESSAR, R. A., UDELL, L., SMUKLER, N., and BOWIE, M. A.
Urine, assay of corticosteroids in, 56, 59
——, excretion of 17-ketosteroids in, in ankylosing spondylitis, 67
—— in Sjögren's syndrome, 67
——, urate excretion in, and phenylbutazone, 317
Urine, uric acid in, in gout, 123, 233
Uricosuric agents and gout, 366
Uterus amputation, arthritis, rheumatoid, and, 341

VAINIO, K. J.: *See* LAINE, V. A. I., VAINIO, K. J., and HOLOPAINEN, T. E.
——: *See* LAINE, V. A. I., VAINIO, K. J., and PEKANMÄKI, K.
Vertebrae, pathology of, 4
Vessels, blood, lesions of, in rheumatic disease, 136
——, calcinosis of, familial 15
Virus, Coxsackie: *See* Coxsackie virus
Von Bechterew's disease: *see* Spondylitis, ankylosing

Walpole, Horace, 195
WARREN, J., 361
WEST, H. F.: Purified ACTH gel : Control of therapy in rheumatoid patients, 56
*——, 74, 351, 352, *373
——, and NEWNS, G. R.: Ankylosing spondylitis and prolonged ACTH therapy, 109
WILSON, G. M.: *See* HUFFMAN, E. R., WILSON, G. M., SMYTH, C. J., and HILL, R.
WILSON, H., *167, 347
*WOLF, M., 167 *bis*
WOODMANSEY, A., 256
World Health Organization, First Report of Expert Committee on Rheumatic Diseases, 253
WYNGAARDEN, B., 347

X-ray Therapy: *See* Radiotherapy

YDÉN, S.: *See* ENGFELDT, B., ROMANUS, R., and YDÉN, S.
*YEOMAN, W., 374
YÜ, T. F., *167, 366

*ZACCO, M., 75
ZIFF, M., *167 *bis*, 347, 352
Zone electrophoresis in study of plasma proteins, 201

2 : 6 dihydrobenzoic acid, 61
9-α-chloro hydrocortisone, 297, 354
9-α-fluoro hydrocortisone acetate, 291, 299, 348
11-oxy-17-ketosteroid, 67
17-ketogenic steroids, 56
—— —— in spondylitis, ankylosing, 109
17-ketosteroids developed from corticosteroids, 56
—— ——, urinary excretion of, 109, 291
—— —— —— in Sjögren's syndrome, 67
—— —— —— in spondylitis, ankylosing, 67, 109

INDEX TO SUBJECTS OF ARTICLES ABSTRACTED

* indicates that only the title of the article is given

Acid, acetylsalicylic, in arthritis, rheumatoid, 79
——, ascorbic, in arthritis, rheumatoid, 80
——, ——, depletion by ACTH with polyphloretin phosphate, 267
——, ——, mephenesin and salicylamide, 381
——, ——, metabolism, ACTH and, 268
——, ——, in rheumatism, acute, 379*
——, diacetylpyrocatchol carboxylic, with cortisone, *276
——, glycyrrhetinic, and cortisone, 386
——, lactic, in osteo-arthritis, 173
——, lysergic, diethylamide in arthritis, rheumatoid, 80
——, *p*-acetylaminosalicylic, in rheumatism, acute, 259
——, *p*-aminobenzoic, in arthritis, rheumatoid, 261
——, —— and cortisone metabolism in liver, 272
——, pyruvic, in blood, steroid therapy and, *276
——, salicylic, action of, *87
——, ——, and hormone therapy, *264
ACTH and adrenal response, 269
—— and —— steroid levels in plasma, 269
—— and —— weight, 98
—— and allergy, 182
—— anaphylactoid reaction, 387
—— and antibody production, 93
—— in arthritis, rheumatoid, 171, 172
—— in arthrosis, *390
—— and ascorbic acid metabolism, 268
—— in asthma, 387
—— and blood, 97, 269, 272
—— and ——, pyruvic acid, *276
—— and bone marrow, 97 *bis*
—— and burns, 275
—— and capillary resistance, *275
—— and carditis, rheumatic, 76
—— in children, *171
—— in chorea minor, 170
—— in dermatomyositis, 174
—— and diabetic mothers, infants of, 272
—— and eosinophil count, 98, *171, 179, 266
—— in exophthalmos, *99
—— in eye disease, 99 *quinter*
—— in —— surgery, 182
——, gastro-intestinal side-effects and, *276
—— and Hamman-Rich syndrome, 274
—— and herpes zoster, *99
—— and keloids, 270
—— and leucocytes, 98
—— in lipoid nephrosis, 388
—— and liver, 94
—— in lupus erythematosus, 85, 271, 386
—— and mental function, 274
—— in nephrosis, 182
—— in neuroretinitis, 99
—— in non-rheumatic conditions, 183
—— and orbital oedema, *99
—— in osteo-arthritis, *84
—— in palindromic rheumatism, *382
—— and *p*-aminobenzoic acid in arthritis, rheumatoid, 80
—— with polyphloretin phosphate, 181, 267
—— and psychiatric risk, 275
—— in ragweed allergy, 182
—— in Reiter's syndrome, 180
—— in rheumatism, acute, 376, *379
—— in shoulder, painful, 265
—— in Still's disease, 82
—— after surgery for arachnoiditis of optic chiasma, 182
—— in tetanus, 388
——, thymus involution test for, 98 *bis*
—— in tuberculosis, pulmonary, 389 *bis*
—— and vitamin-C metabolism, 94
—— withdrawal, 274
Adrenal atrophy due to cortisone, prevented by testosterone, 93
—— cortex activity, assessment of, by assay of urinary 17-keto-steroids, 90
—— —— and colchicine, 97
—— corticoids and concept of rheumatism, *390
—— gland surgery in Cushing's syndrome, 95
——, histology of, 183
Adrenal hyperplasia, cortisone in, 387
—— response to ACTH, 269
Adrenaline and burns, 275
—— cream, test of, 100
Adrenalectomy, urinary steroid excretion after, 179
Adrenocortical function and epinephrine, 94
—— —— in infants of diabetic mothers, 272
—— —— in rheumatism, acute, 76
—— ——, suppression of, by cortisone, 184
—— insufficiency, cortisone in, 269
—— ——, post-operative, after cortisone treatment, 96
—— ——, specific water diuresis test in, 95
—— lipids in experimental pyrexia, *180
—— steroids and eosinopenia, 183
—— syndrome, congenital, cortisone and, 269
Adrenocorticotrophic activity, increase of, 96
Aetiology of rheumatism, 265
Agglutination, sheep cell, *83, *180 *bis*, *266, *385
Agranulocytosis, fatal, due to phenylbutazone, *87
Albers-Schönberg disease, radiology of, *178
Allergy, bacterial, and protein metabolism, cortisone in, 267
——, cortisone in, 99 *bis*
Anaemia of arthritis, rheumatoid, 82
Angioneurotic oedema of orbit, ACTH in, *99
Ankylosing spondylitis: *See* Spondylitis, ankylosing
Antibiotics, cortisone and, 267
Antibody production, experimental, ACTH and, 93
—— ——, ——, cortisone and, 93
Antistreptolysin titre in children, *91
Amidopyrin gentisate in rheumatism, *87 *bis*, 380
p-Aminobenzoate in arthritis, rheumatoid, 79
p-Aminobenzoic acid with ACTH in arthritis, rheumatoid, 80
—— and cortisone metabolism in liver, 272
Aorta, rheumatic stenosis of, commissurotomy for, 376
Appendicular syndrome and rheumatism, *100
Arthritis, chronic, in children, *87
——, ——, pathogenesis of hyperfibrinogenaemia in, *87
——, ——, phenylbutazone in, *379
——, ——, therapy of, *87, 174
——, experimental, cortisone in, *99
——, ——, —— and diethylstilboestrol in, *276
——, gouty, *89 *bis*
——, ——, phenylbutazone in, *264
——, rheumatoid, acetylsalicylic acid in, 79
——, ——, ACTH in, 171, 172
——, ——, —— and *p*-aminobenzoic acid in, 80
——, ——, adrenal hormones in, *87
——, ——, in aged, 172
——, ——, agglutination in, *91, *266, *385
——, ——, anaemia of, 82
——, ——, anthropological data, *83
——, ——, artisone in, *83
——, ——, ascorbic acid in, 80, *379
——, ——, Atebrin in, 81
——, ——, aurothioglycanide (Lauron) in, 79
——, ——, *B*-tetrahydronaphthylamine in, 81
——, ——, and blood, *261
——, ——, and —— sugar, cortisone in, *385
——, ——, cardiac lesions in, *83, *379
——, ——, chloro-amines in, *87
——, ——, citrate iontophoresis in, 378
——, ——, codeine in, 261
——, ——, cortisone in, 171, 261 *bis*, 378, *390
——, ——, —— and nodules in, 266
——, ——, —— with phenylbutazone in, *83
——, ——, diagnosis of, *83
——, ——, electromyography in, *83
——, ——, genetics of, 82
——, ——, gold in, *261
——, ——, glucose-1-phosphate in, 80
——, ——, hand, rehabilitation of, in, 82
——, ——, and heart lesions, *83, *379
——, ——, hormone therapy and urinary steroid excretion in, 79
——, ——, hyaluronidase inhibition in, 174
——, ——, hydrocortisone, intra-articular, in, 92 *ter*, *261
——, ——, hypoglycaemia in, 80

Arthritis, rheumatoid, in industrial medicine, *83
——, ——, iron in, 172
——, ——, laboratory tests for, *91
——, ——, and liver function, *91, 265, *267
——, ——, lysergic acid diethylamide in, 80
——, ——, musculo skeletal function in, *262
——, ——, neurovegetative inquiries in, *262
——, ——, nitrogen mustard in, *379
——, ——, *p*-aminobenzoic acid in, 261
——, ——, —— benzoate in, 79
——, ——, phenylbutazone in, 86, 261, *264
——, ——, placental tissue implantation in, 378
——, ——, polyvalent autovaccines in, *261
——, ——, procaine in, 172
——, ——, prognosis of, *83
——, ——, pulmonary lesions in, 377, *379
——, ——, radiology of, *262
——, ——, —— of chest in coal miners, 260
——, ——, —— of sacro-iliac joint, 173
——, ——, Review of 10 years' literature (Tenth Rheumatism Review, Part I), *178
——, ——, "salimeph-C" in, 381
——, ——, serum agglutination in, *91
——, ——, —— copper in, 179
——, ——, —— iron in, 179
——, ——, and skin, neurovegetative reactivity of, *379
——, ——, ——, thickness of, in hands, *379
——, ——, and spinal osteo-arthritis, *382
——, ——, splenectomy in, 81
——, ——, syndromes of, 377
——, ——, systemic lesions in, 377
——, ——, thiosemicarbazone, 79
——, ——, trypsin in, *261
——, ——, vaccine with chemotherapy in, 172
——, ——, vascular factors in, *379
——, ——, vascularity of subcutaneous nodes in, 91
Arthrography of knee, 177 *bis*
—— of shoulder, *178
Arthropathy, pararheumatic, 85
—— in Reiter's syndrome, *88
Arthrosis, ACTH in, *390
——, cortisone in, *390
—— of shoulder, 172
Artisone in arthritis, rheumatoid, *83
Aschoff bodies in auricular appendages and rheumatic activity, 78
—— —— in diagnosis of rheumatism, acute, 169
Ascitic fluid, 17-hydroxycorticosterone in, 184
Aspirin in rheumatism, acute, 376
Assessment of response of treatment, *178
Asthma, ACTH in, 387
——, bronchial, chloro-amines in, *87
——, epinephrine and, 94
Atebrin: *See* Mepacrine
Aureomycin in erythema exudativum multiforme, *88
—— in rheumatism, acute, 77, 170
Aurothioglycanide (Lauron) in arthritis, rheumatoid, 79
"Aurubin", 378
Auscultation of joints, *88
Autovaccines, polyvalent, in arthritis, rheumatoid, *261

Baastrup's disease: *See* Pseud-arthrosis, interspinous
Backache, benign, *382
Bacteriology, *180
Ballistocardiogram in rheumatism, acute, 259
Basedowian exophthalmos, ACTH in, *99
Bechterew's disease: *See* Spondylitis, ankylosing
B-tetrahydronaphthylamine in arthritis, rheumatoid, 81
Biopsy, liver, in arthritis, rheumatoid, 265
Blood disorders, ACTH and, 272
—— ——, cortisone and, 272
—— ——, phenylbutazone and, 87
—— eosinophils and ACTH, 266
—— and hormone therapy, 97 *bis*
——, peripheral, ACTH and eosinophils in, 179
—— sugar and cortisone, *385
—— vessels in arthritis, rheumatoid, *379
Bone, histology of, *180
—— marrow after hormone therapy, 97 *bis*
Bouillaud's disease, *180
Brucellosis and rheumatism, *382
Burns, ACTH and, 275
——, adrenaline and, 275
——, adrenocortical function and, 275
Bursitis, pathogenesis of, 384
Butazolidin: *See* Phenylbutazone

Capillary permeability and cortisone, 385
—— resistance and steroid therapy, *275
Carditis, rheumatic, corticotrophin in, 76
——, ——, cortisone in, 76
——, ——, disturbances of conduction, *78
——, ——, lesions of, *83, 169, *171, *379
Carditis, rheumatic, hormone therapy in children, 168 *bis*
Cartilage, articular, in osteo-arthritis, 173
——, histology of, *180
——, polarized light studies of, 385
Chemotherapy in arthritis, rheumatoid, 172
Children, antistreptolysin titre in, *91
——, arthritis, chronic, in, *87
——, carditis, rheumatic, in, hormone therapy, 168 *bis*
——, ——, ——, salicylate therapy, 168
—— and collagen disease, serum complement in, 89
——, dermatomyositis in, 174
—— of diabetic mothers, 272
——, disks, protruded lumbar intervertebral, in, 382
——, eczema in, cortisone and, 388
—— and gantrisin tolerance in rheumatism, acute, *78
—— and hyaluronidase-haemoglobin/dispersion test in rheumatism, *385
——, nephrotic, steroid therapy in, 182
——, ocular symptoms in, and rheumatism, 100
—— and rheumatism, acute, ACTH in, *171, *379
——, ——, ——, diagnosis of, 90
——, ——, ——, in infancy, *171
——, ——, ——, prevention of, *260
——, ——, ——, psychology of, in, *78
——, ——, ——, treatment of, 76, 77
Chloramphenicol in Reiter's syndrome, *177
Chloro-amines in arthritis, rheumatoid, *87
Chloroquine sulphate in lupus erythematosus, 262
Chorea, acute, 78
—— minor, ACTH in, 170
—— ——, cortisone in, 170
Chrysotherapy: *See* Gold
Circulation in osteitis deformans, 175
——, skin and peripheral, in rheumatism, 276
Citrate iontophoresis in arthritis, rheumatoid, 378
Coalminers, chest radiology and arthritis, rheumatoid, in, 260
——, rheumatism in, *178
Codeine and cortisone in arthritis, rheumatoid, 261
Cogan's syndrome, *88
Colchicine and adrenal cortex, 97
—— and pituitary gland, 97
——, intravenous, in acute gout, 382
Colchicum autumnale in joint disease, *382
Colinet and Caplan's syndrome, *178
Collagen : chondroitin-sulphate ratio in osteo-arthritis, 173
—— disease in children, serum complement in, 89
—— —— and pulmonary lesions, 381
—— fibrillar structure of cartilage, 385
Commissurotomy, mitral, and rheumatism, acute, 169
—— in rheumatic aortic stenosis, 376
——, rheumatic manifestations provoked by, 390
Compound F: *See* Hydrocortisone
Copper, serum, in arthritis, rheumatoid, 179
Corticoids, urinary, in infants of diabetic mothers, 272
Corticotrophin: *See* ACTH
Cortisone, adrenal atrophy due to, prevented by testosterone, 93
—— and capillary histology, 183
—— and —— hyperplasia, 387
—— and —— system, 269 *bis*
—— and adrenocortical insufficiency, post-operative, 96
—— and allergy, ocular, 99
—— and antibiotics, 267
—— and antibody production, 93
—— antiphlogistic action of, *390
—— in arthritis, rheumatoid, 171, 261, *390
—— in arthrosis, *390
—— in asthma, 273
—— and blood, 97, *385
—— in —— disorders, 272
—— and —— pyruvic acid, *276
—— and bone marrow, 97 *bis*
—— in bronchitis, 273
—— and capillary permeability, 385
—— in carditis, rheumatic, 76
—— in chorea minor, 170
—— and codeine in arthritis, rheumatoid, 261
—— in dermatitis, contact, 181
—— in dermatomyositis, 174
—— and diacetylpyrocatchol carboxylic acid, *276
—— and diethylstilboestrol in arthritis, experimental, *276
—— dosage, 171
—— in eczema, infantile, 182, 388
—— and eosinophil count, 98
—— and erythrocyte sedimentation rate in rheumatism, acute, *171
—— in eye disease, 99 *quinter*, 272, 390 *ter*
—— and gastro-intestinal side-effects, *276
—— and glycyrrhetinic acid, 386
—— and granulation tissue histology, 94
—— and Hamman-Rich syndrome, 274
—— in hay fever, 99
—— in herpes zoster, 272
—— in hypopituitarism, 386

Cortisone in iridocyclitis, 99
—— and keloids, 270
—— and leucocytes, 98
—— and liver, 94, 272
—— in lupus erythematosus, 85, 271, 386
—— and macrophages, 98
—— and metabolic response to injury, 96
—— metabolism in liver tissue, *p*-aminobenzoic acid and, 272
—— in neuroretinitis, 99
—— and nodules, subcutaneous, 266
—— in non-rheumatic conditions, 183
—— in pemphigus, 271
—— and phenylbutazone, *83, 380
—— and pituitary histology, 183
—— and —— somatrophin, 268
——, plasma mucoproteins and protein sugar, *385
—— in pneumoconiosis, 273
—— and polyarthritis, experimental, *99
——, prolonged therapy, *99
——, —— ——, in arthritis, rheumatoid, 378
——, —— ——, in spondylitis, Marie-Strümpell, 84
—— and protein metabolism in bacterial allergy, 267
—— in pseudohermaphroditism, 387
——, psychiatric risk and, 275, *276
—— and reticuloendothelial phagocytosis of streptococci, 267
—— and retrobulbar neuritis, *99
—— in rheumatism, acute, 376
—— in sarcoidosis, 91
—— in shoulder, painful, 264, 265
——, side-effects of, *276
—— in Sjögren's syndrome, *99, *275
—— and sodium compounds, 270
—— in spondylitis with iridocyclitis, *99
—— in Still's disease, 82
—— and synovial fluid, *275, *276
—— and testicular development, 387
—— and testosterone, 93
——, topical, in contact dermatitis, 181
—— in tuberculosis, experimental pulmonary, 389 *bis*
—— in ——, ocular, 390
—— and tumours, experimental, 270
—— and vitamin-C metabolism, 94
—— withdrawal, 274, *275
—— —— in rheumatism, acute, *171
—— acetate after adrenalectomy, 179
—— —— in arthritis, rheumatoid, 261
C-reactive serum protein and rheumatism, acute, 258
Creatinine therapy, 378
Cushing's syndrome, adrenal gland surgery in, 95

Deaths after steroid withdrawal, 274
Dental sepsis and rheumatism, *100
Dermatitis, topical cortisone in, 181
Dermatomyositis in children, hormone therapy, 174
Diabetes in infants of diabetic mothers, 272
Diagnosis, differential, in rheumatism, 276
Dibenylethylenediamine-dipenicillin in prophylaxis of rheumatism, acute, *377
Diethylstilboestrol and cortisone in experimental arthritis, *276
Disk syndrome, 178, *264 *bis*
——, intervertebral, hernia of, *178
——, ——, lumbar, *88
——, ——, ——, protruded, in children, 382
——, ——, pathology of, *264
Diuresis test in adrenocortical insufficiency, 95
Dupuytren's contracture, pathology of, 179
—— ——, radiotherapy in, 176
Dupuytren, reputation of, 99
Dysarthria, developmental, 263
Dysphagia in spondylosis, cervical, 178

Eczema, cortisone in, 182
——, infantile, cortisone in, 388
Effusion in knee joint, *262
Eggs and rheumatism, acute, 259
Electrolytic metabolism in gout, 178
Electromyography in diagnosis of arthritis, rheumatoid, *83
Electrophoresis of blood proteins in rheumatism, acute, 169
Eosinopenia, glucocorticosteroids, reticulo-endothelial system and, 266
——, steroids and adrenomedullary hormones and, 183
Eosinophils in blood and marrow, ACTH and, 179, 266
—— count, ACTH and, 98
—— ——, cortisone and, 98
Epicondylitis, *178
Epinephrine and adrenal cortical function, 94
—— tolerance in asthma, 94
Erythema exudativum multiforme, *88 *bis*
—— —— —— and virus infections, 175
Erythrocyte sedimentation rate and plasma viscosity, *385
—— —— —— in synovium, *180

Excretion, urinary steroid and hormone therapy in arthritis, rheumatoid, 79
Eye disease, ACTH in, 99
—— ——, cortisone in, 99 *quinter*, 272, 390 *ter*
—— ——, hydrocortisone in, 273
—— lesions in gout, 88 *bis*
—— symptoms in children with rheumatism, *83, 100

Felty's syndrome, 81
Femur, radiology of head of, *382
——, vascular anatomy of head of, 84
Fibrositis, *265

Ganglion, gasserian, procaine infiltration of, in arthritis, rheumatoid, 172
Gantrisin, tolerance by children in rheumatism, acute, *78
Gaucher's disease, haematology of, 384
—— ——, splenectomy in, 384
Genetics of arthritis, rheumatoid, 82
Geriatrics, radiology of femoral head in, *382
——, rheumatism acute, in older patients, 376
Gland, pituitary, and colchicine, 97
Glucocorticosteroids, reticulo-endothelium and eosinopenic reaction to, 266
Glucose-1-phosphate in arthritis, rheumatoid, 80
Glycyrrhizin after adrenalectomy, 179
Gold therapy, 378, *379
—— —— in arthritis, rheumatoid, *261
—— —— in palindromic rheumatism, *382
Gout, colchicine, intravenous, in, 382
——, eye lesions in, 88 *bis*
—— in men, *264
——, metabolic studies of electrolytes, 178
——, primary and secondary, 383
——, phenylbutazone in, *89, 264 *bis*, 383
——, sodium salicylate in, 88, *383
——, treatment, 89 *quater*
Granulation tissue, histology of, tissue and cortisone therapy compared, 94
Granulocytopenia after phenylbutazone, *382
Granuloma, rheumatic, pathogenesis of, 89
Group-A *B*-haemolytic streptococcus allergy and arthritis, rheumatoid, 259
GT50: *See* Vitamin D_2

Haematology of arthritis, rheumatoid, *261
—— of Gaucher's disease, 384
Hamman-Rich syndrome, 274
Hand, arthritis, rheumatoid, of, 378
——, rehabilitation in arthritis, rheumatoid, 82
——, skinfold thickness of, in arthritis, rheumatoid, *379
Hay fever, oral cortisone in, 99
Heart disease: *See* Carditis
Heparin and hyperfibrinogenaemia, *87
—— in rheumatism, acute, 258
Herpes zoster, cortisone in, 272
—— —— ophthalmicus, ACTH in, *99
Hip, arthritis of, intra-articular injections in, *173
——, congenital dislocation of, 83
—— derangements in cerebral palsy, 83
——, osteo-arthritis of, *262
——, pseudo-polyarthritis of, 265
Histology of adrenal and pituitary, cortisone and, 183
—— of granulation tissue, 94
Hormone, adrenomedullary, and eosinopenia, 183
—— therapy in carditis, rheumatic, 168 *bis*
—— ——, minimal doses, in hyaluronidase, *264
—— —— in rheumatism, acute, *260
—— —— in rheumatology, *99 *bis*
—— —— and salicylic acid, *264
—— —— and spa treatment, *100
—— —— and urinary steroid excretion in arthritis, rheumatoid, 79
Hyaluronidase-haemoglobin dispersion test, *385
—— inhibition in arthritis, rheumatoid, 174
—— in rheumatic disease, *382
Hydrocortisone, action of, 268, *390
—— in eye diseases, 273
——, intra-articular, 92 *ter*, 180, *264, 271
—— injections in sarcoidosis, 91
—— in rheumatology, 91, *99 *bis*
——, oral, in arthritis, rheumatoid, *261
—— in osteo-arthritis, *84
—— in shoulder, painful, 264
—— in soft-tissue lesions, 181
—— acetate, intra-articular, *275 *bis*, *276, 385
—— —— in periarthritis of shoulder, 270
Hydrocortone: *See* Hydrocortisone
Hypercortisonism and withdrawal syndrome, *275
Hyperfibrinogenaemia, pathogenesis of, in arthritis, rheumatoid, *87
——, placental thromboplastin and, *87
Hypoglycaemia in arthritis, rheumatoid, 80
Hypopituitarism, cortisone in, 386

Industry, arthritis, rheumatoid, and, *83
Injury, metabolic response to, and cortisone, 96
Iontophoresis, citrate, in arthritis, rheumatoid, 378
"Irgapyrin", toxicity of, *177 *bis*
Iritis, gouty, 88
Iron, intravenous, in arthritis, rheumatoid, 172
——, serum, in arthritis, rheumatoid, 179

Joint, auscultation of, *88
——, sternoclavicular in rheumatism, 384

Keloids, ACTH in, 270
——, cortisone in, 270
Keratitis, non-syphilitic interstitial, and deafness with peri-arteritis nodosa, *88
Ketonic fractions in urinary steroid excretion, 79
Knee, arthrography of, 177
——, cartilage studied with polarized light, 385
—— effusion in osteo-arthritis, *262
—— jerk, loss of, in sciatica, *178
——, osteo-arthritis of, *84
——, tomography of, 177

Laboratory studies of hormone therapy, *99
Lauron: *See* Aurothioglycanide
Leucocytes, phagocytic activities of, cortisone and, 98
——, —— ——, ACTH and, 98
Leukergy in locomotor disturbances, *100
Liver biopsy in arthritis, rheumatoid, 265
——, cortisone metabolism in, and *p*-aminobenzoic acid, 272
—— function in arthritis, rheumatoid, *91 *bis*, *267
—— —— in rheumatism, acute, *83
——, weight and composition of, and ACTH, 94
——, —— ——, and cortisone, 94
Locomotor lesions and leukergy, *100
Lung lesions in arthritis, rheumatoid, 377, *379
—— —— in collagen disease, 381
Lupus erythematosus, ACTH in, 85, 271, 386
—— ——, acute, nitrogen mustard in, 86
—— ——, chloroquine sulphate in, 262
—— ——, cortisone in, 85, 271, 386
—— ——, disseminated, natural history of, 85 *bis*
—— ——, mepacrine in, 174
—— ——, ocular lesions, 381
—— ——, splenectomy in, 262
—— ——, triethylene melamine in, 86
Lymphadenitis abdominal, *382

Macrophages, phagocytic activities of, ACTH and, 98
——, ——, cortisone and, 98
Manipulation of shoulder, 265
Marie-Strümpell's disease: *See* Spondylitis, 84
Marrow, ACTH and eosinophils in, 179, 266
—— histology in osteitis deformans, 180, *180
Massage, value of, 100
Mental function, ACTH and, 274, 275
—— ——, cortisone and, 275, *276
Mepacrine in arthritis, rheumatoid, 81
—— in lupus erythematosus, 174
Mephenesin, salicylamide and ascorbic acid, 381
Metabolism of ascorbic acid, ACTH in, 269
—— of cortisone in liver, *p*-aminobenzoic acid and, 272
—— of electrolytes in gout, 178
—— of protein and cortisone in bacterial allergy, 267
——, response of, to injury, 96
—— and salicylate, 381
Microbe therapy of polyarthritis, *382
Muscle spasm, stigmonene bromide in, 263
Musculo-skeletal function in arthritis, rheumatoid, *262
Myelopathy and cervical osteo-arthritis, *264
Myocarditis in rheumatism, acute, 168

Nephrosis, steroid therapy in, 182 *bis*
——, lipoid, ACTH in, 388
Nerves, splanchnic, procaine infiltration of in arthritis, rheumatoid, 172
Neuroretinitis, cortisone in 99
Neurovegetative inquiries in arthritis, rheumatoid, *262
Nitrogen mustard in rheumatism, acute, *379
—— —— in lupus erythematosus, 86
Node, subcutaneous, vascularity of, 91
Nodules, subcutaneous, cortisone and, 266

Osteitis deformans, bone marrow histology in, 180
—— ——, cardiac output in, 175
—— ——, peripheral circulation on, 175
—— pyogenic, radiology of, 175
Osteo-arthritis, 83, 172, 173, *173 *bis*, *262 *bis*
——, ACTH in, *84
——, cervical, myelopathy and, *264
——, collagen changes in cartilage, 173
—— of hip, *173, *262
Osteo-arthritis, hydrocortisone in, *84
—— of knee, *84, *262
——, lactic acid in, 173
——, phenylbutazone in, 84
——, radiotherapy in, *173
Osteogenesis imperfecta, histology of, *180
Osteoporosis, senile, of spine, 176

Paget's disease: *See* Osteitis deformans
Pain and cervical spondylosis, *88, *382
Palindromic rheumatism, gold and ACTH in, *382
Palsy, cerebral, and hip derangements, 83
PAS in rheumatism, acute, *377
—— in tuberculosis, pulmonary, 389
Pemphigus, oral cortisone in, 271
Penicillin in rheumatism, acute, 76
Periarteritis nodosa with Cogan's syndrome, *88
—— —— and rheumatism, *88
Periarthritis, *178
——, humero-scapular, 265, 270
Phagocytosis of streptococci, effect of cortisone on reticuloendothelial, 267
Phenylbutazone, *87, 380, *381 *bis*
—— in arthritis, rheumatoid, 86, 261, *264, 379
—— ——, with cortisone, *83
—— in gout, *89, *264, 264 *bis*, 383
—— in joint disease, *178
—— in osteo-arthritis, 84
——, parenteral, 263
—— in spondylitis, *264
—— in Stevens-Johnson syndrome and granulocytopenia, *382
——, toxicity of, 87 *ter*
——, ——, and blood level, 263
Phospholipid serum, in rheumatism, acute, 259
Phosphorus, radioactive, in tissue analysis in rheumatism, acute, *83
Physiotherapy, value of, 100
Pirisal: *See* Amidopyrine gentisate
Pituitary, histology of, 183
—— therapy in rheumatology, *99
Placental tissue implantation in arthritis, rheumatoid, 378
Plasma adrenal steroid levels, ACTH and, 269
—— mucoproteins and protein sugar, effect of cortisone, *385
—— proteins, electrophoresis of, in rheumatism, acute, 169
—— viscosity and erythrocyte sedimentation rate, *385
Pneumoconiosis and arthritis, rheumatoid, 260
Polyarthritis, microbe therapy of, *382
—— in rubella, *382
Polyphloretin phosphate with ACTH, ascorbic acid depletion by, 267
Polysaccharide, group-A precipitin in streptococcosis and rheumatism, acute, 90
Procaine, infiltration of nerves with, in arthritis, rheumatoid, 172
Protein, C-reactive, in serum in rheumatoid, arthritis, 258
—— metabolism and bacterial allergy, cortisone in, 267
——, plasma and serum, electrophoresis in rheumatism, acute, 169
Prothrombin time in rheumatism, acute, 383
Pseudo-arthrosis, interspinous, *264
Pseudohermaphroditism, cortisone in, 387
Pseudo-polyarthritis of hip and shoulder, 265
Psychogenic rheumatism, *382 bis
Psychology of children with rheumatism, acute, *78
Pyrexia, experimental, adrenocortical lipids in, *180

Radiology of Albers-Schönberg Disease, *178
—— of arthritis, rheumatoid, *262
—— of chest in coal miners and arthritis, rheumatoid, 260
—— of femoral head, *382
—— of osteitis, pyogenic, 175
—— of osteoporosis of spine, 176
—— of sacro-iliac joint, 173
—— of sarcoma, osteoblastic osteogenic, 176
Radiotherapy in Dupuytren's contracture, 176
—— in osteo-arthritis, *173
—— (deep *x*-ray) in spondylitis, 379
Ragweed-allergy, ACTH in, 182
Rehabilitation of hand in arthritis, rheumatoid, 82
Reiter's syndrome, *88 *bis*
—— ——, ACTH in, 180
—— ——, chloramphenicol in, *177
Research in rheumatism, *382
Reticuloendothelial phagocytosis of streptococci, cortisone and, 267
Reticuloendothelium and eosinopenic reaction to glucocorticosteroids, 266
Retrobulbar neuritis, cortisone in, *99
Rheumatic fever: *See* Rheumatism, acute
Rheumatism, acute, *p*-acetylaminosalicylic acid in, 259
——, ——, ACTH in, 376, 379
——, ——, adrenocortical function in, 76
——, ——, in the aged, 376
——, ——, agglutination in, *83
——, ——, allergy in, 259
——, ——, aspirin in, 376
——, ——, aureomycin in, 77, 170

Rheumatism, acute, in children, ACTH and, *171, *379
——, ——, comparative therapy, 376
——, ——, cortisone in, 376
——, ——, —— withdrawal, *171
——, ——, C-reactive serum protein in, 258
——, ——, diagnosis, 90, *180
——, ——, and eggs in diet, 259
——, ——, in Egypt, *171
——, ——, electrophoresis of blood proteins, 169
——, ——, erythrocyte sedimentation rate and hormone therapy in, *171
——, ——, follow-up study of, 260
——, ——, gantrisin in, *78
——, ——, Group-A polysaccharide precipitin reactions in, 90
——, ——, heart conduction disturbance in, *78
——, ——, heparin in, 258
——, ——, hormone therapy in, *260
——, ——, in infancy, *171
——, ——, liver function in, *83
——, ——, and myocarditis, non-specific, 168
——, ——, PAS in, *377
——, ——, pathogenesis of, *260
——, ——, penicillin in, 76
——, ——, prevention of, in children, *78, 170, *171 *bis*, *260, *377
——, ——, prothrombin time in, 383
——, ——, and psychological reactions in children, *78
——, ——, reactivation after mitral commissurotomy, 169
——, ——, serum antistreptolysin-levels in diagnosis of, 90
——, ——, —— diphenylamine reaction in, 77
——, ——, —— phospholipid, 259
——, ——, sodium salicylate in, 77
——, ——, —— ——, and PAS in, *377
——, ——, sulphonamides in, 76
——, ——, tissue analysis with radioactive phosphorus, *83
——, classification of, *100
——, chronic, serology of, *91
Rheumatoid arthritis: *See* Arthritis, rheumatoid
Rubella, polyarthritis in, *382
Rubidium-gold-creatinine-gold in rheumatic disease, 378

Sacro-iliac joint, radiology of, 173
Salicylamide with mephenesin and ascorbic acid, 381
Salicylate in carditis, rheumatic, in children, 168
—— and metabolism, 381
——, percutaneous, experimental, *382
"Salimeph-C" in arthritis, 381
Sarcoma, osteoblastic osteogenic, 176
Sarcoidosis, hormone injections into skin lesions, 91
—— and neuroretinitis, hormone therapy in, 99
Sciatica and dilatation of epidural veins, *88
——, traction in, *178
——, loss of knee jerk in, *178
Scleroderma, 86
Serology of chronic rheumatism, *91
Serum agglutination in arthritis, rheumatoid, *91
——, antistreptolysin-O, levels in diagnosis of rheumatism, acute, 90
—— complement in children with collagen disease, 89
——, C-reactive protein in, and rheumatism, acute, 258
—— diphenylamine in rheumatism, acute, 77
—— iron and copper in arthritis, rheumatoid, 179
—— phospholipid and rheumatism, acute, 259
—— proteins, electrophoresis of, in rheumatism, acute, 169
Sex hormones in rheumatology, *100
Shoulder, arthrography of, *178
——, arthrosis of, 172
——, checkrein, 265
——, "frozen", 265
——, painful, cortisone in, 264
——, periarthritis of, hydrocortisone acetate in, 270
——, pseudo-polyarthritis of, 265
Silicosis, pulmonary, and rheumatism, *178
Sjögren's syndrome, cortisone in, *99, *275
Skin, neurovegetative reactivity of, in arthritis, rheumatoid, *379
—— in spondylitis, ankylosing, *379
—— test with "Trafuril", 86
——, thickness of, in hand in arthritis, rheumatoid, *379
Sodium diacetyl pyrocatechol carboxylate, and pyrocatechol carboxylate, synergism with cortisone, 270
—— salicylate, 92
—— —— and cortisone, *178
—— —— in gout, 88, *383
—— —— in rheumatism, acute, 77, *377
Somatrophin, pituitary, in infections favoured by overdosage of cortisone, 268
Spa treatment and hormone therapy, *100
Splenectomy in arthritis, rheumatoid, 81
—— in Gaucher's disease, 384
—— in lupus erythematosus, 262
Splenomegaly, 384
Spine, senile osteoporosis of, 176
Spondylitis, ankylosing, diagnosis, *379
——, ——, late forms of, *262
——, ——, periarticular soft-tissue changes in, *174
——, ——, skin in, *379
——, ——, and tuberculosis, pulmonary, *262
——, cervical, pain with, *88
——, cortisone in, 84
—— with iridocyclitis, cortisone in, 99
——, phenylbutazone in, *264
——, radiology of, 173
——, radiotherapy in, 379
Spondylosis, cervical, dysphagia and, 178
——, ——, pain and, *382
—— hyperostotica, 85
Stenosis, mitral, Aschoff bodies in diagnosis, 78
——, ——, and rheumatism, acute, 169
Steroid content of ascitic fluid, 184
—— therapy, *276
——, urinary excretion of, after adrenalectomy, 179
——, —— ——, in arthritis, rheumatoid, and hormone therapy, 79
Still's disease, 172
—— ——, hormone therapy in, 82
—— ——, ocular symptoms in, *83
Stevens-Johnson syndrome, *88 *ter*
—— —— —— phenylbutazone, *382
Stigmonene bromide and muscular spasm, 263
Streptococcal infections and rheumatism, acute, *171
Streptococci, cortisone and reticuloendothelial phagocytosis of, 267
Streptococcosis, Group-A polysaccharide precipitin reactions in, 90
Streptomycin in pulmonary tuberculosis, 389 *ter*
Styloiditis, *178
Succinate-salicylate in arthritis, *178
Sulphonamides in rheumatism, acute, 76
Surgery in rheumatoid heart conditions, 376
Sydenham, Thomas, 276
Synovial membrane permeability, *382
Synovium, erythrocyte sedimentation rate in, *180
——, cortisone and, *276
——, hydrocortisone and, *276

Talalgia, study of, *264
Tetanus, ACTH in, 388
Testicle development and cortisone, 387
Testosterone in prevention of adrenal atrophy due to cortisone, 93
Thiosemicarbazone in arthritis, rheumatoid, 79
Thromboplastin, placental, and hyperfibrinogenaemia, *87
Thymus involution test for ACTH, 98 *bis*
Tissue analysis by radioactive phosphorus, *83
Tissue, connective, clinical study of, 89
—— therapy and histology of granulation tissue, 94
Tomography of knee, 177
Tophus, conjunctival, in gout, 88
Toxicity of "Irgapyrin", *177 *bis*
—— of phenylbutazone, 87 *ter*
—— —— and blood level, 263
Toxin, heparinoid, and hyperfibrinogenaemia, *87
"Trafuril" skin test in rheumatic diseases, 86
Triethylene melamine in lupus erythematosis, 86
Trochanteritis, *382
Trypsin in arthritis, rheumatoid, *261
Tuberculosis, ocular, cortisone in, 390
——, pulmonary, ACTH in, 389 *bis*
——, ——, chemotherapy in, 389 *bis*
——, ——, experimental, ACTH in, 389
——, ——, ——, streptomycin in, 389 *bis*
——, ——, ——, cortisone, 389
——, ——, and spondylitis, ankylosing, *262
Tumours, experimental, cortisone and, 270

Ulcer, gastric, due to phenylbutazone, *87
Urine, assay of 17-ketogenic steroids in, in assessing adrenocortical activity, 90
——, corticoid excretion in, as test of adrenocortical function in infants of diabetic mothers, 272
——, steroid excretion in hormone therapy, 79

Vaccine treatment in arthritis, rheumatoid, 172
Vein, epidural, in sciatica, *88
Vitamin B_{12} in rheumatism, 276
Vitamin-C metabolism, ACTH and, 94
—— ——, cortisone and, 94
—— D_2 in chronic joint disease, *87

Waaler-Rose reaction, *267, *385

17-ketogenic steroids, urinary, assay of, in assessing adrenocortical activity, 90
17-ketosteroids after adrenalectomy, 179

INDEX TO AUTHORS OF ARTICLES ABSTRACTED

* indicates that only the title of a paper or article is given

Aber, G. M., 183
Abrams, W. B., 259
Adams, W. S., 94
*Ahringsmann, H., 265
*Alameri, E., 180
Albertini, A. von, 89
*Alegre Marcet, C., 276
*Alés Reinlein, J. M., 385
*Alexander, R., 266
Alfonso, G., 182
*Alyea, W. S., 261
*Amil, M., 84
Anderson, A. B., 273
Anderson, A. E., 274
*Andersson, E., 84
*Andreini, A., 267
Andrews, G. A., 179
*Antoniewicz, E., 171
Archimbaud, J., 177
Arlet, J., 262, *382
*Armstrong, J. R., 88
*Arnold, R., 178

*Badin, J., 385
Bagnall, A. W., 84, 99
Báguena, J., 93
Báguena, R., 93
Bailey, C. P., 376
Baker, F., 82
Ball, K., 387
*Ballabio, C. B., 171
*Barbaso, E., 262
*Barceló, H., 382
Barceló, P., *89 *bis*, *264
*Barceló Torrent, P., 276
Barritt, A. S., 261
Bartfeld, H., 382
Baserga, R., 270
Bassett, S. H., 178
Batterman, R. C., 79
Bauer, F., 178
*Bauer, J., 264
Bauer, W., 171
Bayles, T. B., 86
Bayliss, R. I. S., 269
Bayrd, E. D., 384
Beerman, H., 91
Beigelman, P. M., 86
Bennett, G. A., 266
Bennett, W. A., 96, 183
Berdier. A., 168
Bergin, J. H. E., 176
Berkowitz, S., 385
Bertolani, F., 259
Bevans, M., 377
*Bianchi, C., 382
*Bickel, G., 99
*Birenbaum, A., 88
Björk-Lund, S. I., 272
*Blanch Terradas, F., 172
Bland, M. N., 94
Bland, W. H., 94
*Bloch-Michel, H., 178
Böhmig, R., 384
Böni, A., 92
Boistesselin, R. du, 94
Boland, E. W., *178, *261
Bolton, H. E., 376
Bombelli, R., 97
Bonamour, G., 88
Bond, W. H., 86
*Bonduelle, M., 264
Bonnet, I., 83
Bonnet, P., 83
*Bonniot, R., 264
Booij, C. J., 273
*Bosch Olives, V., 88
Bouissou, H., 168
Bourel, M., 92, *99
Bouvrain, Y., 390
*Bovo, G., 78
Boyne, A. W., 96
Brailsford, J. F., *173, 262
*Brazelton, T. B., 78
Brendstrup, P., 179
Brodie, B. B., 380
Bronstein, J., 385
Brown, B., 383
Brown, E. M., *264, 271
Bruck, E., 263
*Brusch, C. A., 178
Brux, J. de, 94
Buechner, H. A., 274
*Bulgarelli, R., 377
Bunim, J. J., 91, *178, *382
Burns, J. J., 380
*Busch, J., 173
*Butka, K., 100

Cadman, E. F. B., 85
Callahan, A., 99
*Cambier, J., 99
Campbell, R. M., 96
*Camdiani, G., 88
Caplan, A., 260
Capra, R., 173, 270
Cara, J., 387
*Carcassi, U., *91
Cartesegna, F., *180, *379
*Caruso, A. C., 379
Casademont, M., *264, *276
*Castagnoli, M., 178
*Cerimele, E., 87 *bis*
Certonciny, A., 265
Chandler, G. N., 183
Chaouat, Y., 172
Cheli, E., 388
Chenkin, T., 380
Chesley, G. L., 259
*Chevallier, J., 99
*Chiorboli, E., 379
Christie, G. S., 377
Clark, E. J., 376
Clark, W. S., 171
Clawson, B. J., 267
Clayton, B. E., 268
*Clerens, J., 178
Coburn, A. F., 77
Cochran, J. B., 381
Cochrane, A. L., 260
Cochrane, T., 174, 262
Coers, R. J., 273
Cohen, H., 85, 96
Cohen, J., 174
*Cohen, M., 264
Colombi, C., 390
*Conestabile, E., 87
Conrad, A. H., 271
Consden, R., 89
Constable, B. J., 94
Cook, C. D., 174
Cooke, R. A., 182
Cope, C. L., 184
Copeman, W. S. C., 378
*Costa Bertani, G., 100
Coste, F., 92, 172
Court, D., 263
*Coutu, L.-L., 276
Coventry, M. B., 264
Coyer, A. B., 378
Crabbe, J., 98
*Crain, D. C., 178
Cudkowicz, L., 381
Curtarelli, G., 97
Cuthbertson, D. P., 96
Cyriax, J., 181

*Dale, M., 84
Dalgaard, O. Z., 80
Daneo, V., *100, *180, *267, *275, *276, *379, *385
*Daniels, R. S., 171
Dauby, J., 270
Dave, B. T., 388
Davies, H. R., 379
Davis, A. E., 265
Davis, J. S., 382
*Dearing, W. H., 276
Debeyre, J., 177
Debeyre, N., 91
Decker, J. P., 78
*Decourt, J., 99
*Décourt, L., 379
Delbarre, F., 92
Demartini, F., 377
Denis, A., 92
Dent, R. V., 176
*Dickgiesser, F., 180
*Dilling, N. V., 87
*Dimson, S. B., 172
Djian, A., 177, *178
Dodds, C., 378
Dods, L., 387
*Dollfus, M. A., 99
*Dörffel, E., 178
*Dorgan, J. A., 178
*Douthat, A., 382
*Dubois-Poulsen, A., 99
Ducommun, P., 268
Ducommun, S., 268
*Durupt, L., 100
*Dussy, J., 275

Easson, E. C., 379
*Eastham, R. D., 385
Edholm, O. G., 175
Ehring, F. J., 381
*Ehrlich, M., 264
Einaudi, G., *262, *267, *385
Eisler, M., 96
*Elghammer, H. W., 78
Ellis, L. B., 169
Ellman, P., 381
*El Ramly, Z., 171
*El-Sherif, A., 171
Elster, S. K., 386
*Engleman, D. P., 178
*Ensign, D. C., 89
Epstein, N., 76
Essellier, A. F., 266
*Eyquem, A., 91

*Farneti, P., 261
Fearnley, M. E., 263, 378
Ferciot, C. F., 262
Ferencz, C., 76
Ferey, D., 182
*Fernandes, J. M., 379
*Fernández del Vallado, P., 385
*Fernández y Fernández, M., *99, *275
*Fernando, P. B., 379
*Ferond, M., 390
Ferriman, D. G., 273
*Fiebig, W., 382
*Filogamo, G., 276
Fine, M., 99
Finney, R., 176
Finzi, N. S., 174
Fischer, F., 181
Fleminger, J. J., 275
*Florentin, P., 379
*Follis, R. H., 180
*Forest, G. K. de, 266
Forestier, J., 265
Forsyth, C. C., 82
Fortin, P., 390
Fourman, P., 269
*Fournier, A., 262
Frain, J. B., 271
Franceschini, P., 99
*Francesconi, M., 78
*Françon, J., 99
Françon, F., *100, *382
Freedman, A. L., 180
Freedman, H. H., 96
Freeland, D., 86
Friedman, H. H., 85
Friis-Hansen, B., 181
*Frölich, D., 91
*Fry, R. J., 84
Fuchs, U., 172

Galan, E., 182
*Galmiche, P., 275
Garai, O., 273
García, O., 182
García Faez, O., 182
*Gassot, B., 264
Gaudin, G., 383
*Gaufroy, B., 260
*Gautier, A., 87
Gelfand, M. L., 272
Gelli, G., 168
Georg, J., 181
*Gervay, F., 172
*Giardulli, A., 88
Gigglberger, H., 174
Ginsburg, I. W., 79
*Gitelson, S., 276
Gleason, I. O., 384
Glick, S., 258
Glover, R. P., 169
*Glyn, J., 385
Glyn, J. H., 378
Glynn, L. E., 89
Goelkel, A., 172
Goldman, A., 380
Goldner, F., 86
*Goldstein, A. S., 83
*Goobar, J. P., 382
Goodman, H. C., 80
*Goodson, W. H., 261
Gordon, D. M., 273
*Graber-Duvernay, J., 172
Graham, W., *178, *265
*Grasse, L. A., 178
*Gray, J. W., 87
Greene, R., 273
Greenhouse, J., 271
*Grichener, A., 100
Grifone, J. W., 376
*Gsell, O., 83
*Guck, J. K., 88
Guirao Pérez, M., 385
*Gulotta, G. A., 171
Gutman, A. B., 383

*Haas, W. R., 88
Hävermark, N. G., 97
Hain, K., 76
Hamburg, D. A., 274
Hamerman, D. J., 386
Haninger, J., 77

Harken, D. E., 169
*Harmston, G. J., 88
*Harris, L. H., 379
Harris, L. J., 94
Harrison, M. H. M., 84
Hart, F. D., *178, 386
*Harter, F., 180
Hartfall, S. J., 183
*Hartmann, F., 264
Harvey, G., 174, 262
Haserick, J. R., 271
Hastrup, B., 181
Hawn, C. Van Z., 78
Heather, A. J., 79
Helper, H. N., 76
*Hembrow, C. H., 173
Henderson, L. L., 77
*Henriksen, E., 99
Henry, W. L., 183
*Hernandez, F. A., 276
Hersh, A. H., 82
Herxheimer, H., 273
Higgins, C. C., 95
Hirschfeld, I., 258
Holder, R., 78
Hollander, J. L., 180, *264, 271
Hollevoet, —, 88
Hollinger, N. F., 90
Holst, J. E., 80
Homan, J. D. H., 273
Houghton, L. E., 389
*House, F. B., 84
Houser, H. B., *171, 376
*Hošuték, J., 87
Horava, A., 268
Horler, A. R., 269
Howarth, S., 175 *bis*
Hudson, B., 80
Hudson, P. B., 179
Hughes, R. E., 94
Hurlock, B., 184

*Ibrahim, M., 171 *bis*
*Irby, R., 264
Ishibashi, H., 382
Isémein, L., *172, *262

Jackson, R. L., 169
Jacqueline, F., *91, 382
Jamison, W. L., 376
Janeway, C. A., 89
*Janson, P., 177
Janton, O. H., 169
Jawetz, E., 267
Jeanjean, Y., 93
Jeffrey, M. R., 82, 172
*Jennings, G. H., 383
Jessar, R. A., 85, *264
Joag, G. G., 388
*Jochem, E., 91
Johnson, A. L., 76
Johnson, H. M., 262
Jones, M. H., 83
Jones, R., 91
*Josenhans, G., 276
*Justin-Besançon, L., 262

Kaiser, G. D., 266
Kalbak, K., 181
*Kalliomäki, L., 171
*Kaminester, C. E., 88
Kassirskaya, E. G., 265
*Keating, F. R., 96, 184
Kecmanović, Z., 272
*Keenan, G. F., 178
Kellie, A. R., 79
Kelly, H. G., 169
Kennedy, M. C. S., 273
Kennedy, R. L. J., 382
Kern, A. B., 270
Kersley, G. D., 377
*Kieliotis, W., 171
Kilpatrick, G. S., 260
Kishimoto, S., 99
Kitchell, J. R., 376
Kleinberg, W., 96
*Kono, M., 382
*Kresbach, E., 87
*Kreutzer, R., 171
*Kuipers, R. K. W., 275
Kulka, J. P., 171
*Kurtz, C. M., 78
Kuschner, M., 169
Kuzell, W. C., 383

Labourdette, J. M., 182
Lamont-Havers, R. W., 85
*Lang, F. J., 178
Langendorf, R., 168
Larson, E., 180
Laurent, F., 172
Lawrence, J. S., 100, 173
Lee, P. R., 380
Van Leeuwen, L., 273
*Lefkovitz, A. M., 83
Lehtinen, L., 79
*Lehtinen, M., 379
*Lentini, D., 261
Leonard, J. C., 87, 386
Lepri, G., 390
*Leshin, N., 88
Leslie, A., 94
Levernieux, J., 263
Levieff, L., 169
Levin, M. H., 178
Levis, S., 270
Lévy-Lebhar, J. P., 177, *178
Lewis, A., 275
*Lewis, G. W., 382
Lewis, R. A., 388
*Lewitus, Z., 382
*Liess, G., 178
Lièvre, J.-A., *178, *264
Lintz, R. M., 378
*Lima, M. C., 379
*Lockie, L. M., 178
*Lövgren, O., 83
*Lofty Abdel Rahman, M., 171 *bis*
Long, D. A., *260, 267
*Louyot, P., 379
Lovell, R. R. H., 80
Lowell, F. C., 99
Lowman, E. W., 380
Lubschez, R., 76
Lubow, H., 170
Lucherini, T., *87, *97, *100, 180
Lüderitz, B., 81
Lukić, D., 272
*Lutembacher, R., 180
*Lyons, A. R., 379

*Macinot, —, 379
*Mackiewicz, S., 180
McCall, M. F., 182
McCluskey, R. T., 91
McCue, C. M., 260
McIntosh, H. W., 84, 99
*MacKnight, J. C., 264
McNeely, W. F., 169
McSwiney, R. R., 268
McVay, L. V., 170
Mainoli, S., 380
*Maisondieu, M., 275
*Malaguzzi Valeri, C., 87
Malitz, S., 274
Malkina, M. G., 78
*Mancini, B., 381
Mankle, E. A., 383
Mann, P., 179
*Manzanares, E., 100
Maranon, G., *99, *275
*Marczynska-Robowska, M., 379
Marini, C., 388
Marson, F. G. W., 88
Marti, H. R., 266
Marticke, G., 262
Martin, G. J., 96
Martin, J. R., 98
Mason, R. M., 264
Mathews, S. S., 83
Matteis, F. de, 258
Di Matteo, J., 390
Matthews, B. F., 173
*Maurice, P., 385
Maycock, R. L., 91
*Mayerhofer, F., 87
Meanock, I., 263
Medical Research Council, Panel on the Haematological Applications of ACTH and Cortisone, 272
—— —— —— Sub-committee, 261
Medoff, A. S., 384
*Melloni, F., 381
Menichini, G., 168
*Merrick, E. Z., 87
Merrill, E. R., 267
Methot, —, 168
Meyer, K. A., 81
Miall, W. E., 260
*Miccoli, G., 261
*Michel, R., 88
Michotte, L. J., 270
Miller, H., 263
Milne, M. D., 176
Milošević, B., 272
Mittelman, A., 179
Mizukawa, T., 99
Modell, S., 274
Moeschlin, S., 93, 98
*Moffatt, J. L., 382
Molchanova, L. A., 100
Montgomery, M. M., *178, 266
*Montserrat, S., 382 *bis*
Moore, L. V., 77
*Van Moorleghem, J., 172
Morandi, L., 266
*Moreau, G., 262
*Moreno, A. R., 276
Morgan, T. E., 389 *bis*
Morley, M., 263
Movitt, E. R., 265
Mulholland, H. F., 263
Muller, G. M., 83
*Muratore, F., 178

Nadell, J., 377
*Nakayama, T., 382
*Nassim, J. R., 87
*Natale, P., 87
Natenshon, A. L., 381
Natterer, G., 84
Naugler, W. E., 383
Neligan, G. A., 175
Nerenberg, S. T., 267
Neustadt, D. H., *264, 385
Neutelings, J. P. H., 273
*Neuwirth, E., 178
*Newman, M. K., 83
Newns, G. R., 171
Nichols, H. T., 376
Nordenson, N. G., 97
Norymberski, J. K., 90
Nuffield Foundation Joint Committee on Cortisone and ACTH in Chronic Rheumatic Diseases, 261
*Nyfos, L., 99

*O'Brien, D. J., 381
O'Connell, J. H., 263
Oka, M. J., 81, 86, *171
Oldham, P. D., 260
Oleesky, S., 95
Oliner, L., *88, 183
O'Neill, T. J. E., 169
*Ono, M., 382
*Örström, A., 83
*Ortona, L., 377
Ory, M., *173, *276
Osborne, J. A., 80
Ott, V. R., 85
Den Oudsten, S. A., 273
Overbeek, G. A., 273

Panigatti, F., 258
*Pannewitz, G. von, 173
Pap, L. de 92
Pasquariello, G., 385
Patel, D. J., 258
Patel, J. C., 388
Patley, H., 263
Pattee, C. J., 98
Pavlov, N. M., 100
*Paylan, A., 88
Peabody, J. W., 274
Pemberton, M., 261
Pérez-Stable, M., 182
*Peterman, E. A., 87 *bis*
*Petersen, K. Birkum, 84
*Peterson, W. L., 171
*Picchio, A., 174
Piccinelli, O., 380
*Pierson, B., 379
*Pilkington, T., 87
*Pirtkien, R., 379
*Platoff, G. E., 87
*Plügge-Heidelberg, H., 83
Pohl, W., 378
*Porro, F., 381
*Poulin, J. E., 99
Poutasse, E. F., 95
Prader, A., 269
*Preston, R. L., 262
*Prévot, A.-R., 261
Prosiegel, R., 172
Prunty, F. T. G., 268
*Puig Leal, J., 385

Quigley, T. B., 265

Ragan, C., 85, *178, 377
*Raimondo, F. di, 87
Ramey, E. R., 183
*Ramirez Gilbon, J., 99
*Ramunni, M., 178
Randall, C. C., 175
*Ravault, P., 88
*Rechenberg, H. K. von, 83
*Redon, M., 172
Riising, P. V., 80
Rivo, J. B., 178
*Rizzente, S., 382
Robbins, S. L., 78
Robecchi, A., 173, 270, *275
Roberts, E., 76
Robin, J., 91, 92
*Robinson, D., 87
Robinson, R. C. V., 181
*Robinson, W. D., 178
Rohn, R. J., 86
Rohrschneider, W., 381
*Rome, H. P., 276
Ronchese, F., 270
Root, S. W., 179
*Ropes, M. W., 178
*Rose, D. L., 261
*Rosenberg, E. F., 178
Rossi, G., *261, *262, *379
*Rossing, P., 382
Roussak, N. J., 176
Routh, J. I., 169
*Rouveix, J., 260
Roy, J., 182
Rubens-Duval, H., 262
Rubinstein, M. A., 180
Rusoff, J. H., 258

Salassa, R. M., 96, 184
Sáns Sola, L., *89 *bis*, *382
Saphir, O., 168
*Sardini, G., 377
*Sargent, A. F., 178
*Saslaw, M. S., 276
Satoskar, R. S., 388
*Sauer, W. G., 276
Savage, O., 378
Scalabrino, R., 97, 385
Schaal, K., 84
Schaffarzick, R. W., 383
Schiller, I. W., 99
*Schirmer, K., 390
*Schliephake, E., 100
*Schlossmann, K., 83
Schmid, J., *83, *91, *390
*Schneider, H., 178
*Schnitzer, A., 177
Schwartz, M., 181
Schwartz, S., 85
Schwartzman, J., 170
*Scuro, L. A., 377
*Secondo, G., 100
Seddon, H. J., 83
Selye, H., 268
*Serane, J., 264
*Serra, A. Peralba, 89
*Severens, J. M., 180
Sevitt, S., 275
Sèze, S. de, 91, 92, 177, *178, 263
*Shapira, T. M., 88
Sharp, G., 96
Sharp, J., 379
Sheehan, H. L., 386
Sherman, W. B., 182
Shubik, P., 270
*Sichére, R. M., 264
*Siebenmann, R., 99
*Sigler, J. W., 89

Sikula, L., 77
Silver, M., 385
Singer, B., 182
Sladden, R. J., 100
*Slocumb, C. H., 275
Smelin, A., 180
Smith, D. T., 389 *bis*
Smith, E. K., 169
*Smyth, C. J., 178
*Snow, W. G., 87
*Sobhy, M., 99
Soffer, L. J., 386
Sokoloff, L., 91, 384
Soloff, L. A., 169
Solomon, W. M., 82
Solomons, B., 388
Someya, K., 382
*Sorour, A., 171
Soulié, P., 390
Sperling, S. C., 83
Sprague, R. G., 96, 184
Sprechler, M., 181
Sprunt, D. H., 170
*Srbová, D., 87
Stanier, W. M., 89
Stark, H., 390
*Stawecki, J., 83
Stecher, R. M., 82
Steck, I. E., 266
*Steel, S. J., 382
*Steele, C. W., 83
Steele, J. M., 380
Steinbeck, A. W., 269
Steiger, W. A., 79
Steinberg, C. LeR., 81
Steinbrocker, O., 85, *264, 385
Steiner, G., 176
*Stepantzchitz, G., 87
Sterne, J., 383
Stewart, J. S., 276
Stollerman, G. H., 258
Stolzer, B. L., 376
Storey, G., 86, *381
Stubbs, R. D., 90
*Suarez, Gonzalez, 172
Sugihara, H., 382
Sullivan, R. D., 91
Summa, C., 97, *180 *bis*
Summers, V. K., 386
Suzue, T., 99
*Svartz, N., 83
Svien, H. J., 382
Swift, S., 387

Takagi, Y., 99
*Talbot, B., 78
*Talbott, J. H., 89
*Tarnopolsky, S., 382
*Taubenhaus, M., 88
*Taylor, A. R., 382
Teixeira, M. A., 92
*Telkkä, A., 379
Thing, E., 98 *bis*
Thompson, M., 86
Tonning, H. O., 171
*Toone, E. C., 264
Traynor, J. A., 84
*Treichler, J., 382
Tricot, R., 390
Troisier, O., 181
Trubek, M., 85
Trueta, J., 84
*Trutschel, W., 91
Turiaf, J., 93
Turner, P. P., 273
Udell, L., 271
*Uehlinger, E., 99
Uhrbrand, H., 266
Unanue, E., 182

Vaughan-Morgan, J., 273
Veraguth, P., 382
*Verges, G., 276
Viergiver, E., 259
Van der Vies, J., 273
*Vignon, G., 88
*Vilaseca, J. M., 264
Villiaumey, J., 262
Vines, R., 387
Virkkunen, M., 79
Vollmer, H., 182
Volpicelli, M., 97, *180 *bis*

Wade, A. P., 79
*Wager, O., 180
*Wahl, M., 390
*Wall, P., 83
Wallis, A. D., 259 *bis*
Wang, P., 169
Wanzer, S. H., 389 *bis*
Warmong-Larsen, A., 181
Warren, R. F., 179
Warrick, C. K., 175
*Warum, F., 390
*Wasz-Hockert, O., 91
*Watkins, A. L., 83
Webb, J. H., 382
Wedgwood, R. J. P., 174, *174
Weidmann, H., 267
*Weil, M.-P., 264
Weiss, R. S., 271
Weiner, M., 380
Weinstein, L., 90
Weissenbach, R., 92
Welch, R. G., 82
*Wells, B. B., 91
*Werblow, S. C., 276
West, H. F., 90, 171
*Wetheimer, P., 88
*Wheatley, D., 177
Wiener, S., 76
Wiesel, L. L., 261, 272
*Wijenaike, W., 379
*Wildholm, O., 91
Wilkins, L., 387
*Wilkoszewski, E., 171
Wilson, M. G., 76
Wilson, W. M. G., 99
*Wolf, J., 88
*Wollaeger, E. E., 276
Wolpaw, R., 82
Womack, C. R., 175
Wulff, H., 181

*Yoshida, T., 382
Yourish, N., 88

*Zacco, M., 390
Zaontz, J. B., 170
Zarafoneits, C. J. D., 79
Zatichni, J., 169
*Zinn, W., 178
Zivin, S., 266
Zizine L., 93
Zoeckler, S. J., 180
Zurukzoglu, W., 98